CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215596Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	NDA 215596
Priority or standard	Priority
Submit date(s)	3/23/2021
Received date(s)	3/23/2021
PDUFA goal date	11/23/2021
Division/office	Division of Antivirals (DAV)
Review completion date	Click or tap to enter a date.
Established/proper name	Maribavir
(Proposed) proprietary name	Livtencity
Pharmacologic class	Cytomegalovirus (CMV) pUL97 kinase inhibitor
Code name	TAK-620
Applicant	Takeda Pharmaceuticals USA., Inc.
Dosage form(s)/formulation(s)	Tablet
Dosing regimen	400 mg orally twice daily (BID)
Applicant proposed indication(s)/ population(s)	Treatment of adults with post-transplant cytomegalovirus (CMV) infection and/or disease, including infections resistant and/or refractory to ganciclovir, valganciclovir, cidofovir, or foscarnet.
Proposed SNOMED indication	28944009 |Cytomegalovirus infection (disorder)|
Regulatory action	Approval
Approved dosage (if applicable)	400 mg BID
Approved indication(s)/ population(s) (if applicable)	Livtencity is indicated for the treatment of adults and adolescents (12 years of age and older weighing at least 35 kg) with post-transplant cytomegalovirus (CMV) infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir, or foscarnet
Approved SNOMED term for indication (if applicable)	28944009|Cytomegalovirus infection (disorder)|

Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED, Systematized Nomenclature for Medicine

Table of Contents

Table of Tables

Table of Figures

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
API	active pharmaceutical ingredient
AUC	area under the concentration-time curve
AUC_{ss}	AUC from 0 to 24 hours on the last day of exposure
BCRP	breast cancer resistance protein
BID	twice daily
BMI	body mass index
bp	base pairs
CAP/CTM	COBAS® AmpliPrep/COBAS® TaqMan® CMV Test
CD	cluster of differentiation
CI	confidence interval
CL/F	apparent clearance
CLcr	creatinine clearance
C_{max}	maximum plasma concentration
$C_{max,ss}$	maximum concentration on the last day of exposure
CMH	Cochran-Mantel-Haenszel
C_{min}	minimum plasma concentration
CMV	cytomegalovirus
CSR	clinical study report
C_{trough}	lowest plasma concentration
CYP	cytochrome P450
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
EC_{50}	half-maximal effective concentration
eCRF	electronic case report form
E-R	exposure-response
GD	gestation day
GI	gastrointestinal
GLP	good laboratory practices
HCMV	human cytomegalovirus
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplant
IAT	investigator-assigned treatment
ICH	International Conference on Harmonisation
IIV	interindividual variability
IND	investigational new drug
IR	information request
ITT-S	intent-to-treat safety
IU	international units
IV	intravenous
K_a	dissociation constant
Ki	inhibitory constant

LLOQ	lower limit of quantification
LOAEL	lowest observed adverse effect level
NDA	new drug application
NOAEL	no observed adverse effect level
OSI	Office of Scientific Investigations
PBPK	physiological based pharmacokinetic
PCR	polymerase chain reaction
PFA	phosphonoformate
P-gp	P-glycoprotein
PK	pharmacokinetic
PMR	postmarketing requirement
PND	postnatal day
PopPK	population pharmacokinetic
PWR	Pediatric Written Request
Q/F	apparent intercompartmental clearance
qPCR	quantitative polymerase chain reaction
QTc	corrected QT interval
RAS	resistance-associated substitution
RHD	recommended human dose
SAE	serious adverse event
SEAP	secreted alkaline phosphatase
SOC	system organ class
SOT	solid organ transplant
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TID	thrice daily
ULN	upper limit of normal
USPI	United States Prescribing Information
Vc/F	apparent volume of distribution in the central compartment
Vp/F	apparent volume of distribution in the peripheral compartment

I. Executive Summary

1. Summary of Regulatory Action

The new drug application 215596 for maribavir was submitted by Takeda Pharmaceuticals on March 23, 2021. Maribavir is a first-in-class cytomegalovirus (CMV) pUL97 kinase inhibitor. The new drug application was reviewed by the multidisciplinary team. The review team considered the originally proposed indication, "Livtencity is indicated for the treatment of adults with post-transplant cytomegalovirus (CMV) infection and/or disease, including infections resistant and/or refractory to ganciclovir, valganciclovir, cidofovir, or foscarnet," too broad, as only limited data were submitted in support of maribavir for treatment of non-resistant or non-refractory CMV, and there is an ongoing trial in this population. Overall, the review team recommended approval of maribavir for a more limited indication: the treatment of adults and adolescents (12 years of age and older weighing at least 35 kg) with post-transplant CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir, or foscarnet. Although there was some initial disagreement within the review team regarding the appropriate action, at the conclusion of review, the Statistics Reviewer did not object to approval for this limited indication, but voiced the opinion that due to the history of the drug (failure in two well-controlled prophylaxis trials), it would have been preferrable to review results from both Phase 3 trials (302 and 303) instead of only Trial 303 before approval of maribavir.

I, the signatory authority for this application, concur with the recommendations to approve for a more limited population. An Advisory Committee panel, convened on October 7, 2021, agreed unanimously with approval of maribavir for treatment of resistant or refractory CMV infection/disease. Maribavir will be approved for the treatment of adults and adolescents (12 years of age and older weighing at least 35 kg) with post-transplant CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir, or foscarnet (Section II.6.2).

The Applicant submitted a single Phase 3 trial and a supportive Phase 2 trial in post-transplant solid organ or hematopoietic stem cell recipients with CMV infection/disease refractory to treatment (with or without genotypic resistance) to ganciclovir, valganciclovir, foscarnet, or cidofovir. Although there were some concerns with the open-label Phase 3 trial design and possible selection bias, the Advisory Committee panel acknowledged the difficulties in conducting a double-blind trial in this population. The available safety data show that maribavir is safe for its intended use. I concur that identified risks can be mitigated through labeling and further evaluated through postmarketing surveillance and required postmarketing studies. The overall benefit-risk is favorable, as described in Table 2. For detailed information on the basis of this approval, please refer to the detailed reviews included in this document and the Product Quality Review.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Approximately 45,000 solid organ or hematopoietic stem cell transplants are performed every year in the United States. • Cytomegalovirus (CMV) is the most frequent opportunistic pathogen in transplant recipients, contributing to both patient morbidity and mortality. About one third of overall transplant recipients will have CMV infection. • A subgroup (5% to 25%) of transplant patients with CMV infection become refractory to treatment (with or without genotypic resistance) with currently available drugs (ganciclovir, valganciclovir, foscarnet or cidofovir). • The subgroup of patients with refractory CMV infection/disease is associated with higher morbidity and mortality compared to patients with susceptible CMV infection/disease.	CMV infection/disease refractory to treatment is a significant cause of morbidity and mortality in transplant recipients. Of greatest concern is the subgroup of transplant recipients with CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with currently available drugs (ganciclovir, valganciclovir, foscarnet or cidofovir) because of the higher rate of morbidity and mortality (Avery et al. 2016; Fisher et al. 2017).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Currently there are no FDA-approved drugs for the treatment of post-transplant CMV infection/disease or for the treatment of postransplant CMV infection/disease refractory to treatment (with or without genotypic resistance) to drugs used off-label for these indications. • Patients with mild or moderate CMV infection are treated with oral valganciclovir, whereas patients with severe infection are generally treated with intravenous ganciclovir. • Treatment of patients with refractory CMV infection/disease is very challenging due to absence of controlled clinical trials to help select the best alternate treatment. Existing treatment algorithms are based on consensus expert opinion (Kotton et al. 2018; Razonable and Humar 2019; Yong et al. 2021). • If severe CMV infection/disease is present, most experts recommend the addition or switching to foscarnet. — If disease is not severe, most experts recommend full or high dose intravenous ganciclovir. — Definitive antiviral therapy is based on genotypic resistance testing and clinical response. — If no resistance-associated substitutions are detected, treatment with ganciclovir is generally continued and emphasis is given to optimization of drug dosing and host factors rather to switching antivirals. Immunosuppressive medicines shoud be decreased to the lowest feasible amount. • Currently available drugs are associated with a relatively toxic safety profile.	There is an urgent need for new anti-CMV drugs which are: • Effective for the treatment of CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with currently available dugs. • Less toxic than currently available drugs used off- label for this indication. • Easily administered (orally).
Benefit	• The efficacy of maribavir for the treatment of of CMV infection/disease refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, foscarnet or cidofovir was established in one Phase 3 trial (Trial 303) and supported by one Phase 2 trial (Trial 202). • The primary endpoint in Trial 303 was the proportion of subjects with confirmed CMV viremia “clearance” defined as unquantifiable plasma CMV DNA (<LLOQ; i.e., <137 IU/mL) at the end of Week 8. The key secondary efficacy endpoint was CMV viremia clearance and CMV infection symptom control at the end of Week 8 with maintenance of this treatment effect through Study Week 16. The results are shown below.	Despite the limitations of the open-label design of the trial and concerns for bias, Trial 303 showed that maribavir, at 400 mg BID adninistered orally for 8 weeks, significantly increases the proportion of subjects with undetectable CMV DNA levels at the end of treatment (Week 8) in comparison to investigatory assigned treatment.

Dimension	Evidence and Uncertainties	Conclusions and Reasons

Table 3. CMV Viremia Clearance at Week 8

CMV Viremia Clearance at Week 8	Maribavir N=235 n (%)	IAT N=117 n (%)
Primary endpoint: CMV DNA <LLOQ at Week 8		
Responders	131 (56)	28 (24)
Adjusted difference in proportion of responders (95% confidence interval)[a]		33 (23, 43)
P-value, adjusted[a]		<0.001
Key secondary endpoint: CMV DNA <LLOQ and CMV infection symptom control at Week 8 with maintenance through Week 16		
Responders	44 (19)	12 (10)
Adjusted difference in proportion of responders (95% confidence interval)[a]		9 (2, 17)
P-value, adjusted[a]		0.02

Source: Statistics Reviewer's Analysis
[a] Mantel-Haenszel weighted average approach was used for the adjusted difference in proportions (maribavir-IAT), the corresponding 95% confidence interval, and the p-value, adjusting for the transplant type and baseline CMV DNA level. Only those with both stratification factors were included in this computation.
Abbreviations: CMV, cytomegalovirus; DNA, deoxyribonucleic acid; IAT, investigator-assigned treatment; LLOQ, lower limit of quantitation; N, number of subjects in study arm; n, number of subjects within specified category

- Efficacy was supported by the results of a Phase 2 dose-ranging trial comparing 3 doses of maribavir in a population similar to the Phase 3 trial. Although there was no comparator arm and no dose response among the three treatment groups, antiviral activity was demonstrated and the response rate in the treatment groups was similar to that observed in the Phase 3 trial in the same population.
- Efficacy in adolescents (12 years of age and older weighing at least 35 kg) is extrapolated from efficacy in adults in the Phase 3 trial, 303, for the 400 mg BID dose and predicted similar maribavir exposures in adults and adolescents based on modeling and simulation.

Risk and Risk Management	• The safety database is based primarily on the Phase 3 trial (Trial 303) and supportive safety data from the Phase 2 trials (Trials 202 and 203).The safety population in Trial 303 is comprised of 352 subjects: 236 subjects in the maribavir group and 116 in the investigator-assigned treatment (IAT) group. A total of 224 subjects in this trial received maribavir 400 mg BID for at least 45 days: 202 subjects in the maribavir arm and 22 subjects in the IAT arm who switched to the rescue arm. An additional 124 subjects from the two Phase 2 trials received maribavir 400 mg BID or higher doses for at least 56 days.. • Taste disturbance, nausea, diarrhea, vomiting and fatigue were the most commonly adverse events reported in >10% of the patients in the Phase 3 trial. • The Applicant conducted numerous drug-drug interaction studies to characterize the impact of maribavir on concomitant medications and vice versa. • Maribavir has a low genetic barrier to resistance as many virologic failure subjects had treatment-emergent resistance-associated substitutions in pUL97 and pUL27. Several pUL97 valganciclovir/ganciclovir resistance-associated substitutions confer cross-resistance with maribavir and some maribavir resistance-associated substitutions in pUL97 confer cross-resistance with valganciclovir/ganciclovir. • When maribavir was tested in combination with other antiviral compounds, antagonism of the antiviral activity was seen in combination with valganciclovir/ganciclovir.	• Considering that resistant/refractory CMV infection/disease in transplant patients is serious and life-threatening and that maribavir has received an orphan drug designation and breakthrough therapy designation, a safety database of approximately 300 patients is considered adequate. • Maribavir demonstrated an overall favorable safety profile. Taste disturbance (dysgeusia, ageusia, hypogeusia, taste disorder) was the most common adverse event with the use of marivabir. The frequency of taste disturbance was much higher in the maribavir group compared to the IAT group (46% versus 4%). Nausea, diarrhea, vomiting and fatigue occurred at a similar rate as in the IAT group. It should be noted that taste disturbance rarely led to discontinuation of maribavir. • Product labeling adequately addresses drug-drug interactions with recommendations on how to avoid or on how to manage interactions. • Data with respect to resistance and cross-resistance have been added to the product label and adequately address the concerns. The Applicant agreed to characterize additional ganciclovir/valganciclovir resistance-associated amino acid

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		substitutions for cross-resistance with maribavir as postmarketing requirments. • Product label adequately addresses the antagonism of antiviral activity seen in combination with valganciclovir/ganciclovir.

Abbreviations: BID, twice daily; CMV, cytomegalovirus; DNA, deoxyribonucleic acid; IAT, investigator-assigned treatment; LLOQ, lower limit of quantitation

2.2. Conclusions Regarding Benefit-Risk

Currently there are limited therapeutic options for treating or preventing CMV in transplant recipients. As of the writing of this review, only five drugs have received FDA approval for systemic use for treating or preventing CMV disease: letermovir, ganciclovir and its prodrug valganciclovir, foscarnet, and cidofovir. Letermovir is approved for CMV prophylaxis in CMV seropositive hematopoietic stem cell transplant recipients; ganciclovir and valganciclovir are approved for preventing CMV disease in transplant recipients and for treating CMV retinitis in immunocompromised patients, including patients with acquired immunodeficiency syndrome. Foscarnet and cidofovir have received approval for treating CMV retinitis in patients with acquired immunodeficiency syndrome. Moreover, most of these drugs (ganciclovir, valganciclovir, foscarnet, and cidofovir) are associated with significant toxicities. It is noteworthy that no drugs are FDA-approved for the treatment of asymptomatic CMV viremia or for the treatment resistant/refractory CMV infection/disease.

In the absence of controlled clinical trials to help select the best alternate therapy, management of patients with a refractory CMV infection (with or without genotypic resistance) is very challenging. Existing treatment algorithms are based on consensus expert opinion rather than on the results of well-controlled trials. Briefly, when drug resistance is suspected, the first step, if possible, is to decrease the immunosuppressive regimen and test for genotypic resistance. If severe CMV disease is present, most experts recommend the addition of or switching to foscarnet; if disease is not severe, most experts recommend full or high dose ganciclovir. Definitive antiviral therapy is based on genotypic resistance testing and clinical response (Kotton et al. 2018; Razonable and Humar 2019; Yong et al. 2021).

In the Phase 3 pivotal trial (Trial 303) submitted with this new drug application, maribavir was superior to the investigator-assigned treatment for the proportion of subjects with unquantifiable CMV deoxyribonucleic acid levels (less than the lower limit of quantitation) at the end of Week 8. Clearly, this trial had many limitations and there were concerns of potential bias due to the open-label design and the known adverse events associated with the drugs used in the investigator-assigned treatment arm. However, the results of the primary endpoint were further supported by sensitivity analyses of the primary endpoint, subgroup analyses and analyses of the secondary endpoints. The Advisory Committee recognized the limitations and potential bias in Trial 303. They also acknowledged the difficulties in conducting a double-blind trial in this population. Despite these limitations, the Advisory Committee members unanimously recommended the approval of maribavir for the treatment of CMV infection/disease that is refractory (with or without genotypic resistance) with ganciclovir/valganciclovir, foscarnet, or cidofovir.

The safety profile of maribavir demonstrated in the Phase 3 trial and the supportive data from the two Phase 2 trials (Trials 202 and 203) appears to be acceptable. The most significant adverse event associated with the use of maribavir was taste disturbance which was reported in 46% of maribavir-treated subjects. However, this adverse event rarely led to discontinuation of maribavir and it usually resolved while on treatment or after the end of treatment.

Maribavir has a low genetic barrier to resistance. A significant proportion of the subjects who failed the primary endpoint during treatment with maribavir had treatment-emergent amino acid resistance-associated substitutions in pUL97 and pUL27. Furthermore, several of the pUL97

resistance-associated substitutions confer cross-resistance to ganciclovir/valganciclovir and several ganciclovir/valganciclovir resistance substitutions confer cross-resistance to maribavir. Resistance data are included in the product label. Additionally, a warning for virologic failure due to resistance, and recommendations to monitor CMV deoxyribonucleic acid levels during treatment and to check for resistance if patients do not respond to treatment were included in section 5 of the package insert. Furthermore, the Applicant agreed with the Division to characterize additional ganciclovir/valganciclovir resistance-associated substitutions for cross-resistance with maribavir as a postmarketing requirement.

In spite of the deficiencies noted in the pivotal Phase 3 trial (open-label design and potential bias), the efficacy and safety data submitted in this application support the approval of maribavir for the treatment of CMV infection/disease refractory to treatment (with or without genotypic resistance) with currently available drugs. The availability of maribavir will provide a new option for the treatment of these patients who are in urgent need of effective, less toxic, and easily administered drugs.

II. Interdisciplinary Assessment

3. Introduction

The following review issues were identified with this new drug application (NDA).

3.1. Review Issue List

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

3.1.1.1. Does the Phase 3 Trial, SHP620-303, Provide Substantial Evidence of Effectiveness for Treatment of Resistant CMV Infection/Disease?

3.1.1.2. Does the Phase 3 Trial, SHP620-303, Provide Substantial Evidence of Effectiveness for Treatment of Refractory CMV Infection/Disease?

3.1.1.3. Does the Phase 2 Trial, SHP1263-202, Provide Supportive Evidence for the Efficacy of Maribavir for Treatment of Resistant/Refractory CMV Infection/Disease?

(b) (4)

3.1.2. Key Review Issues Relevant to Evaluation of Risk

3.1.2.1. Treatment-Emergent Resistance to Maribavir

3.2. Approach to the Review

Table 4 provides an overview of the clinical trials submitted in the NDA. Results from the Phase 3 trial (Trial 303) provide the primary basis of efficacy and safety of maribavir for the treatment of post-transplant cytomegalovirus (CMV) infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, foscarnet, or cidofovir. Results from the Phase 2 trial (Trial 202) are considered supportive for this indication.

The Applicant also submitted data from Trial 203 (b) (4)

(b) (4)

Table 4. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for Maribavir

Study Number	Study Description	Phase	Subjects Randomized	Number of Centers and Countries
SHP620-303	Multicenter, randomized, open-label, active-controlled study conducted in 352 post-transplant subjects with CMV infection or disease that was refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, foscarnet or cidofovir. Enrolled subjects were randomized in a 2:1 ratio to receive oral maribavir 400 mg BID or investigator-assigned treatment up to 8 weeks. Upon completing treatment, subjects entered a 12-week follow-up period.	3	352 (maribavir: 235, IAT: 117)	Centers: 94 Countries: 12
SHP620-202	Multicenter, randomized, dose-ranging, parallel group study of maribavir conducted in 120 post-transplant subjects with CMV infection or disease that was refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, or foscarnet. Enrolled subjects were randomized in a 1:1:1 ratio to receive oral maribavir 400 mg BID, 800 mg BID or 1,200 mg BID for up to 24 weeks. Upon completing treatment, subjects entered a 12-week follow-up period.	2	120 (maribavir 400 mg BID: 40, 800 mg BID: 40, and 1,200 mg BID: 40)	Centers: 27 Countries: 1 (United States)
SHP620-203	Multicenter, randomized, dose-ranging, parallel group study conducted in 139 post-transplant subjects who had CMV infection without evidence of CMV organ disease or a CMV infection known to be refractory to available anti-CMV drugs. Enrolled subjects were randomized in a 1:1:1:1 ratio to receive oral maribavir at one of three doses (400 mg BID, 800 mg BID or 1,200 mg BID) or valganciclovir (Weeks 1-3: 900 mg BID, after Week 3: 900 mg QD) for up to 12 weeks. Upon completing treatment, subjects entered a 12-week follow-up period.	2	139 (maribavir 400 mg BID: 40, maribavir 800 mg BID: 40, maribavir 1,200 mg BID: 39, valganciclovir: 40)	Centers: 38 Countries: 6

Abbreviations: BID, twice daily; CMV, cytomegalovirus; IAT, investigator-assigned treatment; QD, once daily

4. Patient Experience Data

Two patient-reported outcomes questionnaires (EQ-5D-5L and SF-36v2) were included in the clinical study to measure health-related quality of life. These were completed at the time points specified in the Schedule of Assessments. EQ-5D-5L was completed at baseline and Study Week 4, 8, 12, 16, and 20. SF36v2 was completed at baseline, Study Week 2 4, 6, 8, 12, 16, and 20. The impact of maribavir on quality of life was an exploratory endpoint and therefore is not discussed in this review.

Table 5. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		Not applicable
☒	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Clinical pharmacology properties of maribavir were comprehensively evaluated (Table 6). The clinical pharmacology review focused on the acceptability of physiological based pharmacokinetic (PBPK) modeling to support labeling recommendations for coadministration of maribavir with certain anticonvulsants that are cytochrome P450 (CYP) 3A inducers (carbamazepine, phenytoin, phenobarbital), coadministration of maribavir (inhibitor of breast cancer resistance protein [BCRP] transporter) with substrates of BCRP such as rosuvastatin (Section 8.2), and predicted exposures for patients ≥12 years of age and weighing ≥35 kg (Section 8.3).

Table 6. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
Pharmacologic Activity	
Established pharmacologic class (EPC)	Cytomegalovirus (CMV) pUL97 kinase inhibitor
Mechanism of action	Maribavir inhibits the pUL97 protein kinase activity in a biochemical assay with a 50% inhibitory concentration value of 0.003μM and replication of CMV in cell culture with 50% effective concentration (EC_{50}) values ranging from 0.03 to 2.2μM depending on the cell line and assay endpoint.
Active moieties	Pharmacological effects are due to the parent drug maribavir. The primary metabolite, VP44469, has an EC_{50} value for CMV inhibition that is >100-fold higher than maribavir.
QT prolongation	In a thorough QT study, maribavir 1,200 mg (maximum concentration [C_{max}] ~2× higher than the recommended 400 mg dose) versus placebo resulted in a maximum mean (90% CI) QT interval change of 2.3 milliseconds (-0.1, 4.7), which is not clinically relevant.
General Information	
Bioanalysis	In the Phase 3 study 303, plasma maribavir was measured using a fully validated LC-MS/MS method A7177M-SHP620. The calibration range was 0.2 to 100 μg/mL. Long term storage stability was 2067 days at -20°C and 779 days at -80°C. Several other assays were used for measurement of maribavir in other studies in which PK was assessed (Section III.14.3).
Healthy subjects versus patients	In transplant patients with CMV infections versus healthy subjects, C_{max} is 5% higher and AUC is 27% higher
Drug exposure at steady state following the therapeutic dosing regimen (or single dosage, if more relevant for the drug)	At a maribavir dose of 400 mg BID in transplant patients with CMV, geometric mean (%CV) C_{max} is 17 μg/mL (39%), $AUC_{0\text{-}tau}$ is 128 μg·h/mL (51%), and C_{tau} is 4.9 μg/mL (90%).
Range of effective dosage(s) or exposure	Phase 3 study 303 evaluated a dose of 400 mg BID, where the steady-state 5th to 95th percentiles of PK parameters were the following: 10 μg/mL and 33 μg/mL for C_{max}, 56 μg·h/mL and 273 μg·h/mL for AUC, and 1.1 μg/mL and 20 μg/mL for C_{trough}.

Characteristic	Drug Information
Maximally tolerated dosage or exposure	The highest dose evaluated in Phase 2 studies was 1,200 mg BID, at which there were no safety issues
Dosage proportionality	Maribavir is dose proportional at single doses of 50-1600 mg and at multiple doses of up to 2400 mg daily
Accumulation	Upon single versus multiple twice daily dosing, accumulation ratio (based on comparison of AUC) ranges from 1.24 to 1.49. (based on noncompartmental analysis) and is 1.47 (based on population pharmacokinetic analysis).
Time to achieve steady-state	Two days
Bridge between to-be-marketed and clinical trial formulations	Not applicable as the to-be-marketed tablet formulation was used in Phase 3 study 303. Formulations used in Phase 1 studies included capsules, oral solution, and tablet formulations I to IV.
Absorption	
Bioavailability	The absolute bioavailability of maribavir is unknown
T_{max}, median	1-3 hours
Food effect (fed/fasted) Geometric least square mean and 90% CI	When taken orally with a moderate fat meal versus fasted, the $AUC_{0\text{-}inf}$ and C_{max} (geometric mean ratio [90% CI]) of maribavir are 0.864 (0.804, 0.929) and 0.722 (0.656, 0.793), respectively.
Distribution	
Apparent steady-state volume of distribution, mean	27.3 L
Plasma protein binding	98% across a concentration range of 0.05 to 200 µg/mL
In vitro blood-to-plasma ratio	1.37 across the concentration range of 0.005 to 10 µg/mL
Drug as substrate of transporters	Maribavir is a substrate of P-gp, BCRP, and OCT1
Elimination	
Mass balance results	After a single radiolabeled dose of 400 mg, the percentage of the dose excreted as total radioactivity (unchanged drug) was 61% (<2%) in urine and 14% (5.7%) in feces
Oral clearance (CL/F), mean	2.9 L/h in transplant patients
Half-life, mean	4.3 hours in transplant patients
Metabolic pathway(s)	Maribavir is primarily eliminated by CYP3A4 (major) and CYP1A2 (minor)
Drug-related components in plasma	88% maribavir as unchanged drug during the first 24 hours
Primary excretion pathway	Hepatic metabolism
Intrinsic Factors and Specific Populations	
Body weight	No dosage adjustment is required based on weight, age, mild to severe renal impairment, and mild to moderate hepatic impairment (severe hepatic impairment was not evaluated)
Age	
Renal impairment	
Hepatic impairment	
Drug Interaction Liability (Drug as Perpetrator)	
Inhibition/induction of metabolism	Maribavir is a weak inhibitor of CYP3A
Inhibition/induction of transporter systems	Maribavir is an inhibitor of P-gp and BCRP

Source: Reviewer
Abbreviations: $AUC_{0\text{-}tau}$, area under the curve to the end of the dosing period; $AUC_{0\text{-}inf}$, area under the curve from time zero to infinity; BCRP, breast cancer resistance protein; BID, twice daily; CI, confidence interval; C_{trough}, trough concentration; CYP, cytochrome P450; LC-MS/MS, liquid chromatography-tandem mass spectrometry; OCT1, organic cation transporter 1; P-gp, P-glycoprotein; PK, pharmacokinetics; T_{max}, time to maximum concentration

5.1. Nonclinical Assessment of Potential Effectiveness

The nonclinical data support the effectiveness of maribavir for the treatment of human cytomegalovirus (HCMV) and include the following findings:

- Biochemical and virologic studies characterized the mechanism of action of maribavir; maribavir inhibits the HCMV pUL97 protein kinase activity in a biochemical assay with a half maximal inhibitory concentration of 3nM.
- Maribavir inhibited replication of HCMV in cell culture with half maximal effective concentration (EC_{50}) values ranging from 0.03 to 2.2µM; these concentrations can be achieved in vivo at the proposed dose
- Maribavir showed broad antiviral activity in cell culture against HCMV isolates with different glycoprotein B genotypes.
- Maribavir antagonized the antiviral activity in cell culture of valganciclovir/ganciclovir.
- Genotypic and phenotypic characterization of maribavir-resistant virus confirmed the target of maribavir and indicated that cross-resistance with valganciclovir/ganciclovir is possible. See Section III.18.7.

These nonclinical data (summarized below) supported further clinical development of maribavir.

5.1.1. Mechanism of Action (Study Report V9503M-SHP620)

Maribavir was initially identified in a screen for compounds that inhibit the pUL97 serine protein kinase of HCMV. Maribavir inhibited wild-type pUL97 protein kinase in a biochemical assay with a half maximal inhibitory concentration of 3nM. In contrast, the half-maximal inhibitory concentration of maribavir against the pUL97 kinase with the L397R amino acid substitution from the 2916rA resistant virus was increased 20,000-fold to 60µM, consistent with the maribavir resistance profile.

The activity of maribavir as well as the 5'-mono- and 5'-triphosphate derivatives of maribavir against HCMV deoxyribonucleic acid (DNA) polymerase and human polymerase, delta, were also evaluated in biochemical assays. Enzyme activity was measured by incorporation of ^{3}H-deoxynucleotide triphosphates (namely deoxyadenosine triphosphate, deoxycytidine triphosphate, deoxyguanosine triphosphate, and deoxythymidine triphosphate) into activated calf thymus DNA. Maribavir and its 5′-mono- and 5′-triphosphate derivatives at 100µM had no significant effect on the incorporation of deoxynucleoside triphosphates for both HCMV DNA polymerase and human DNA polymerase, delta. Refer to Section III.18.1 for the complete review of mechanism of action.

5.1.2. Antiviral Activity in Cell Culture (Study Reports V9499-SHP620 and V12150M-TAK-620)

The cell culture antiviral activity of maribavir has been evaluated against HCMV (strain AD169; glycoprotein B [gB] 2 genotype) using various cell lines and assays. The EC_{50} values ranged from 0.03 to 2.2µM depending on the cell line and assay endpoint. The cell culture antiviral activity of maribavir has also been evaluated against HCMV clinical isolates. The median EC_{50}

values were 0.1μM (n=10, range 0.04 to 0.13μM) and 0.28μM (n=10, range 0.12 to 0.56μM) using DNA hybridization and plaque reduction assays, respectively. The antiviral activity of maribavir in a plaque reduction assay was similar for different gB genotypes with median EC_{50} values of 0.33μM (n=2, range 0.28 to 0.38μM), 0.51μM (n=1), 0.44μM (n=4, range 0.34 to 0.45μM), and 0.35μM (n=1) against gB1, gB2, gB3, and gB4, respectively. The distribution of gB genotypes in the population of the United States was reported to be 26 to 50%, 18 to 40%, 23 to 28%, and 4 to 8% for gB1, gB2, gB3, and gB4, respectively (Zipeto et al. 1998; Bale et al. 2000). Refer to Section III.18.2 for the complete review of cell culture antiviral activity studies.

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

6.1.1. Trial SHP1263-202 (Trial 202), SHP1263-203 (Trial 203) and SHP620-303 (Trial 303)

The Applicant conducted exposure-response (E-R) analyses using the data from the two dose ranging studies 202 and 203 that evaluated different doses of maribavir (400, 800, and 1,200 mg twice daily [BID]) for treatment of CMV infections in solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) recipients. E-R analyses were performed by univariate analysis, which included change from baseline in viral load at week 1 and 2 (linear regression), probability of undetectable plasma CMV DNA at any time (logistic regression), and probability of recurrence (logistic regression). No E-R relationship was observed for change from baseline in viral load or probability of undetectable plasma CMV DNA. Taken together, no difference in response between 400, 800, and 1,200 mg BID dose levels was observed in studies 202 or 203, which is supportive of the selection of 400 mg BID for Phase 3 Study 303.

E-R analysis for efficacy was performed using efficacy and pharmacokinetics (PK) data from adult transplant recipients with CMV infections in Study 303 at single dose level (400 mg BID). The PK data were available for a total 254 patients treated with maribavir, including 232 patients assigned to receive maribavir and 22 patients who received maribavir as a rescue therapy. E-R analysis was performed based on a total of 231 patients from the PK set who were enrolled in the maribavir arm and had PK exposure parameters. PK variables were maximum plasma concentration (C_{max}), area under the concentration-time curve (AUC), and lowest plasma concentration (C_{trough}). Efficacy variables were confirmed unquantifiable (less than the lower limit of quantification [LLOQ]) plasma CMV DNA at the end of Study Week 8 (primary endpoint) and the confirmed unquantifiable (<LLOQ) CMV and CMV infection symptom control at Study Week 8 followed by maintenance through Week 16 (secondary endpoint). Logistic regression analyses of E-R were conducted.

In a univariate analysis, probability of confirmed unquantifiable (<LLOQ) plasma CMV DNA at Week 8 (along with the other efficacy variables) decreased with increasing maribavir exposure. This relationship was partly attributed by the greater frequency of treatment-emergent substitutions in those with higher maribavir exposures. In multivariate analyses, treatment-emergent CMV substitutions conferring resistance and cluster of differentiation 4^+ and 9^+ cell count at baseline were identified as significant predictors for the response variable and a shallow but statistically significant decreasing E-R relationship was observed between maribavir AUCs

and the probability of confirmed unquantifiable (<LLOQ) plasma CMV DNA at Week 8. The E-R analyses are described in more detail in Section III.14.4.2.

6.2. Clinical Trials Intended to Demonstrate Efficacy

6.2.1. Trial SHP620-303 (Trial 303)

6.2.1.1. Design, Trial 303

Trial SHP620-303 (Trial 303) was a Phase 3, multicenter, randomized, open-label, active-controlled study designed to assess the efficacy and safety of SHP620 (maribavir) compared to investigator-assigned treatment (IAT) of CMV in HSCT and SOT transplant recipients with CMV infections that were resistant or refractory to treatment with ganciclovir, valganciclovir, foscarnet or cidofovir (Figure 1). Subjects fulfilling the entry criteria were randomized in a 2:1 ratio to receive either maribavir 400 mg orally twice daily or the Investigator-assigned anti-CMV treatment for 8 weeks. To be eligible for the trial subjects had to have documented CMV infection resistant or refractory to anti-CMV drugs with a screening CMV DNA value ≥2,730 international units (IU)/mL in whole blood or ≥910 IU/mL in plasma in two consecutive assessments separated by at least 24 hours, as determined by the local or central lab quantitative polymerase chain reaction (qPCR) testing. Both samples had to be taken within 14 days before randomization with the 2nd sample obtained within 5 days before randomization. Results from the same laboratory and same blood sample (whole blood or plasma) had to be used for the randomization. For the purposes of this trial, resistant and refractory CMV infection were defined as follows:

- Resistant CMV
  - Documented failure to achieve >1 $\log_{10}$ decline in CMV DNA level in whole blood or plasma after an interval of 2 or more weeks of treatment with intravenous (IV) ganciclovir, oral valganciclovir, IV foscarnet or IV cidofovir; and
  - Documentation of one or more CMV resistance-associated amino acid substitutions to ganciclovir/valganciclovir, foscarnet, or cidofovir
- Refractory CMV
  - Documented failure to achieve >1 $\log_{10}$ decline in CMV DNA level in whole blood or plasma after an interval of 2 or more weeks of treatment with IV ganciclovir, oral valganciclovir, IV foscarnet, or IV cidofovir; and
  - Absence of any known resistance-associated amino acid substitutions to ganciclovir/valganciclovir, foscarnet, or cidofovir

Eligible subjects were stratified by transplant type (HSCT or SOT) and the baseline CMV viral load as determined by the most recent local or central laboratory qPCR results available at the time of randomization:

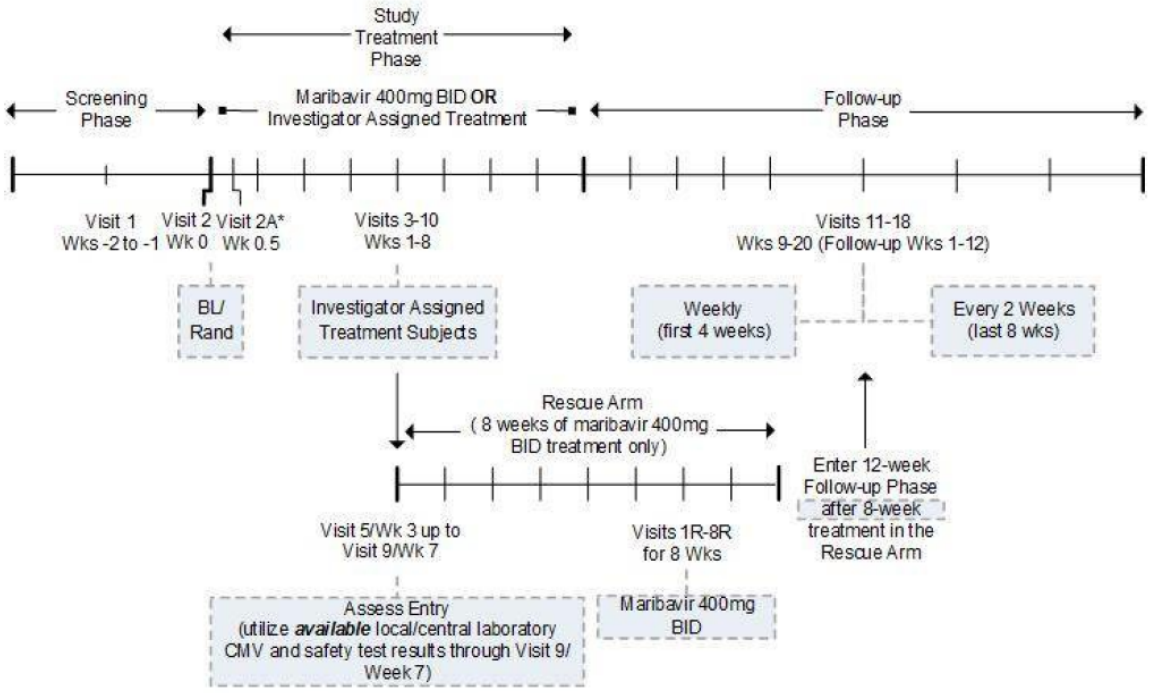
- Low viral load (≥910 IU/mL to <9100 in plasma or ≥2730 IU/mL to <27,300 IU/mL in whole blood).
- Intermediate viral load (≥9,100 IU/mL to <91,000 IU/mL in plasma or ≥27,300 IU/mL to <273,000 IU/mL in whole blood).

- High viral load (≥91,000 IU/mL in plasma or ≥273,000 IU/mL in whole plasma).

Subject enrollment was monitored to achieve an approximate target of 60% subjects with resistant CMV infection whereas the remaining subjects had refractory CMV infection.

The primary endpoint of the trial was the proportion of subjects with undetectable CMV DNA levels at the end of 8 weeks of treatment. The key secondary endpoint was the proportion of subjects who maintained CMV viremia clearance after 8 weeks of treatment through Study Week 16 (8 weeks after study drug discontinuation). It is noteworthy that a cohort of the enrolled subjects had tissue-invasive CMV disease or CMV syndrome at baseline. These subjects were also assessed for the improvement or resolution of the symptoms of the CMV disease or CMV syndrome.

Figure 1. Study Design Schematic, Trial 303



BID=twice daily; BL=baseline; CMV=cytomegalovirus; R=rescue; Rand=randomized; wk=week

[a] Visit 2A/2A(R) was only required for subjects taking tacrolimus, cyclosporine, everolimus, or sirolimus at Visit 2/2R.

Note: Eligibility to enter the maribavir rescue arm was assessed starting at Visit 5/Week 3 up to Visit 9/Week 7.

Source: Figure 1 in the Clinical Study Report.

6.2.1.2. Eligibility Criteria, Trial 303

Inclusion Criteria

A male/female subject who received an HSCT or SOT and had to meet all of the following criteria:

- The subject must have been able to provide written, personally signed, and dated informed consent to participate in the study before completing any study-related procedures. As applicable, a parent/both parents or legally authorized representative must

have provided signature of informed consent and there must be documentation of assent by the subject before completing any study-related procedures.

- The subject must have been ≥12 years on the day of signing the informed consent.
- The subject must have weighed ≥35 kg.
- The subject must have been a recipient of HSCT or SOT
- The subject must have had a documented CMV infection in whole blood or plasma, with a screening value of ≥2730 IU/mL in whole blood or ≥910 IU/mL in plasma in 2 consecutive assessments, separated by at least 1 day, as determined by local or central specialty laboratory qPCR or comparable quantitative CMV DNA results. Both samples should have been taken within 14 days prior to randomization with second sample obtained within 5 days prior to randomization. The same laboratory and same sample type (whole blood or plasma) must have been used for these assessments.
- The subject must have had a current CMV infection that was resistant or refractory to ganciclovir/valganciclovir, foscarnet, or cidofovir (see definitions of resistant or refractory under trial design). The Investigator must have been willing to treat the subject with at least 1 of the available anti-CMV drugs (ganciclovir, valganciclovir, foscarnet, or cidofovir). Note: Combination therapy with foscarnet and cidofovir was not permitted in the IAT arm due to the potential for serious nephrotoxicity.
- Had all of the following results as part of screening laboratory assessments (results from either the central laboratory or a local laboratory could have been used for qualification):
  - Absolute neutrophil count ≥1,000/mm^3 (1.0×10^9/L)
  - Platelet count ≥25,000/mm^3 (25×10^9/L)
  - Hemoglobin ≥8 g/dL
  - Estimated creatinine clearance ≥30 mL/min/1.73m^2
- Had a negative serum beta human chorionic gonadotropin pregnancy test at screening if a female of child-bearing potential. Urine pregnancy tests could be done per institutional requirements. Sexually active females of child-bearing potential must have agreed to comply with any applicable contraceptive requirements of the protocol. If male, must have agreed to use an acceptable method of birth control, as defined in the protocol, during the study treatment administration period and for 90 days afterward the last dose if treated with maribavir, ganciclovir, valganciclovir, or cidofovir and for 180 days afterward if treated with foscarnet.
  Was able to swallow tablets or receive tablets crushed and/or dispersed in water via a nasogastric or orogastric tube.
- The subject must have a life expectancy of ≥8 weeks.
- The subject must have been willing and have an understanding and ability to fully comply with study procedures and restrictions defined in the protocol.

Exclusion Criteria

A subject was not eligible for the study if any of the following criteria were met:

- Had a current CMV infection that was considered refractory or resistant due to inadequate adherence to prior anti-CMV treatment, to the best knowledge of the Investigator.

- Required ganciclovir, valganciclovir, foscarnet, or cidofovir administration for conditions other than CMV when study treatment was initiated (example: herpes simplex virus coinfection requiring use of any of these agents after the randomization) or needed coadministration with maribavir for CMV infection.
  - A subject who was not continuing with the same antiviral drug(s) (ganciclovir, valganciclovir, or foscarnet) for the study treatment (when randomized to the IAT arm), must have discontinued their use before the first dose of IAT. If the subject was currently being treated with cidofovir and was assigned by the Investigator to another anti-CMV therapy as IAT, the subject must have discontinued use of cidofovir at least 14 days prior to randomization at Visit 2/Day 0 and the first dose of IAT.
- Been receiving leflunomide, letermovir, or artesunate when study treatment was initiated.
  - Subjects receiving leflunomide must have discontinued the use at least 14 days prior to randomization at Visit 2/Day 0 and the first dose of study treatment. Subjects receiving letermovir must have discontinued use at least 3 days prior to the first dose of study treatment. Subjects receiving artesunate must have discontinued the use prior to the first dose of study treatment.
- Had severe vomiting, diarrhea, or other severe gastrointestinal (GI) illness within 24 hours prior to the first dose of study treatment that would preclude administration of oral/enteral medication.
- Had known hypersensitivity to the active substance or to an excipient for a study treatment.
- Had tissue-invasive CMV disease with central nervous system involvement, including the retina (e.g., CMV retinitis).
- Had serum aspartate aminotransferase >5× upper limit of normal (ULN) at screening, or serum alanine aminotransferase >5× ULN at screening, or total bilirubin ≥3.0× ULN at screening (except for documented Gilbert's syndrome), by local or central laboratory.

  NOTE: Subjects with biopsy-confirmed CMV hepatitis were not excluded from study participation despite aspartate aminotransferase or alanine aminotransferase >5× ULN at screening.
- Had known positive results for human immunodeficiency virus. Subjects had to have a confirmed negative human immunodeficiency virus test result within 3 months of study entry or, if unavailable, had to be tested by a local laboratory during the screening period.
- Required mechanical ventilation or vasopressors for hemodynamic support at the time of enrollment.
- Been female and pregnant or breast feeding.
- Had previously received maribavir.
- Had received any investigational agent with known anti-CMV activity within 30 days before initiation of study treatment or investigational CMV vaccine at any time.
- Had received any unapproved agent or device within 30 days before initiation of study treatment.
- Had active malignancy with the exception of nonmelanoma skin cancer. Subjects who had a HSCT and who had experienced relapse or progression of the malignancy, as per Investigator's opinion were not to be enrolled.

- Been undergoing treatment for acute or chronic hepatitis C.
- Had any clinically significant medical or surgical condition that in the Investigator's opinion could have interfered with the interpretation of study results, contraindicated the administration of the assigned study treatment, or compromised the safety or well-being of the subject.

6.2.1.3. Statistical Analysis Plan, Trial 303

The primary endpoint was confirmed CMV viremia clearance at Week 8 (end of treatment), defined as plasma CMV DNA concentration <LLOQ (i.e., <137 IU/mL). The primary efficacy analysis took place after the last subject completed the Week 8 visit which was the planned end of treatment visit. For clearance of CMV viremia to be declared at the end of Study Week 8, the subject must have received exclusively study-assigned treatments. Confirmed CMV viremia clearance at the end of Study Week 8 (Visit 10) was defined in the Clinical Study Report as plasma CMV DNA concentrations <LLOQ (i.e., <137 IU/mL), when assessed by COBAS® AmpliPrep/COBAS® TaqMan® CMV Test at a central specialty laboratory, in 2 consecutive postbaseline samples separated by at least 5 days, regardless of whether either study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy as long as subjects did not switch to prohibited anti-CMV or maribavir rescue therapy (see Table 3 in Appendix 15 from investigational new drug [IND] application 51001 SDN 486).

The Applicant's primary efficacy analysis considered subjects with missing data at Week 7 and 8 who achieved confirmed viremia clearance at the time of early discontinuation to be non-responders and as responders in sensitivity analyses. Due to concerns about the open-label design and potential selection biases, the FDA requested that these subjects be classified as responders in the primary efficacy analysis (FDA information request 1 in SDN 486). The FDA stated that this responder definition be considered irrespective of when subjects dropped out of the study or switched to maribavir rescue therapy and that any other considerations could be tested using sensitivity analyses.

The Applicant disagreed and stated that this would conflict with the previous agreement that the timing of assessment of the primary endpoint for clearance of CMV viremia should occur at a fixed timepoint, specifically 8 weeks while on therapy, citing Type C Meeting Minutes on December 7, 2015. Instead, the Applicant agreed to change the primary endpoint to confirmed clearance of plasma CMV DNA at the end of 8 weeks of therapy irrespective of the duration of treatment, provided subjects who discontinued early did not take additional agents for CMV. However, this was not likely to be the case (i.e., subjects would not take additional prohibited anti-CMV agents after early discontinuation of treatment) because of the open-label study design where investigators could actively encourage study subjects to switch to maribavir due to the possibility of lower toxicity compared to IAT.

The key Secondary Endpoint was the achievement of CMV viremia clearance and symptom control at the end of Study Week 8, followed by maintenance of this treatment effect for an additional 8 weeks off treatment (i.e., follow-up Week 16). Criteria for defining the key secondary efficacy endpoint were defined in the statistical analysis plan as:

- First being a responder at the end of Study Week 8, irrespective of study treatment duration, based on CMV viremia clearance and assessment of the tissue invasive CMV disease or CMV syndrome status (i.e., resolution or improvement of tissue invasive CMV disease or CMV syndrome for subjects symptomatic at baseline or no symptoms of tissue invasive CMV disease or CMV syndrome for subjects asymptomatic at baseline).

and

- Maintenance of this treatment effect (both CMV viremia clearance and tissue-invasive disease or CMV syndrome control) through Study Week 16 (see Table 114, from the clinical study report [CSR], in Section III.15 of this review).

As pre-specified in the protocol, the hypothesis testing of the primary and key secondary endpoint was adjusted for multiple comparisons using a fixed sequence testing procedure to control the family-wise Type 1 error rate at α =0.05 level. First, the primary endpoint analysis (CMV viremia clearance at Week 8) was assessed at α =0.05. If and only after this was statistically significant, the key secondary endpoint of response based on maintaining CMV viremia clearance and resolution/improvement/no new development in symptoms after 8 weeks of treatment through Follow-up Week 16 was assessed at α =0.05. If this was statistically significant, it was concluded that the effect of maribavir is more sustainable compared to the control group at Follow-up Week 16 (i.e., 8 weeks off treatment).

Efficacy was pre-specified to be assessed using risk differences (maribavir to IAT) and statistical tests obtained using Cochran-Mantel-Haenszel (CMH) weighted average strata of transplant type (SOT versus HSCT) and baseline plasma CMV DNA level as two stratification factors. Due to a small number of subjects with high baseline plasma CMV DNA levels, the Statistics Reviewer combined high and intermediate strata.

6.2.1.4. Results of Analyses, Trial 303

For Trial 303, demographic characteristics were generally similar between maribavir and IAT groups for race, ethnicity, and median age (Table 7). However, the maribavir group had a slightly higher proportion of male subjects (63% versus 56%) and subjects who were ≥65 years of age (23.0% versus 14%) compared with IAT. Fifty-five percent of randomized subjects were from the United States while the majority of the treatments assigned as part of the regimen after subjects were randomized to IAT were foscarnet, ganciclovir and valganciclovir. Sixty percent of subjects received a solid organ transplant while the majority (over two thirds) of subjects had low CMV DNA viral loads at randomization and 8% of subjects had symptomatic CMV infection as determined by an Endpoint Adjudication Committee.

Table 7. Baseline Demographic and Clinical Characteristics, Safety Population, Trial 303

Characteristic	Maribavir 400 mg BID (N=235)	IAT (N=117)
Sex, n (%)		
Male	148 (63%)	65 (56%)
Female	87 (37%)	52 (44%)
Age, years		
Mean (SD)	53.8 (13)	51.5 (13)
Median (min, max)	57 (19, 79)	54 (19, 77)
Age groups (years), n (%)		
≥17 to <65	181 (77%)	101 (86%)
≥65 to <75	50 (21%)	14 (12%)
≥75	4 (2%)	2 (2%)
Race, n (%)		
White	179 (76%)	87 (74%)
Asian	9 (4%)	7 (6%)
Black/African American	29 (12%)	18 (15%)
Other	16 (7%)	5 (4%)
Missing	2 (1%)	0 (0%)
Ethnicity, n (%)		
Hispanic	14 (6%)	7 (6%)
Non-Hispanic	198 (84%)	95 (81%)
Not reported/unknown	23 (10%)	15 (13%)
Country of participation, n (%)		
United States	127 (54%)	64 (55%)
United Kingdom	11 (5%)	3 (3%)
Italy	0 (0%)	1 (1%)
Belgium	26 (11%)	5 (4%)
Germany	11 (5%)	3 (3%)
Other	60 (26%)	41 (35%)
Treatment(s) used as part of the IAT[a], n (%)		
Foscarnet	N/A	47 (40%)
Ganciclovir	N/A	28 (24%)
Valganciclovir	N/A	28 (24%)
Cidofovir	N/A	6 (5%)
Foscarnet plus valganciclovir	N/A	4 (3%)
Foscarnet plus ganciclovir	N/A	3 (3%)
Transplant type, n (%)		
HSCT	93 (40%)	48 (41%)
SOT	142 (60%)	69 (59%)
CMV DNA		
Low	153 (65%)	85 (73%)
Intermediate	68 (29%)	25 (21%)
High	14 (6%)	7 (6%)
Symptomatic CMV infection by EAC	21 (9%)	8 (7%)

Source: Statistics Reviewer's analysis.
[a] Specific IAT after randomization
Abbreviations: BID, twice daily; CMV, cytomegalovirus; EAC, Endpoint Adjudication Committee; IAT, investigator-assigned treatment; N, number of subjects in treatment group; HSCT, hematopoietic stem cell transplant; n, number of subjects with given characteristic; SOT, solid organ transplant

Of the 415 subjects screened, 63 (15%) were screening failures resulting in a total of 352 randomized subjects (Table 8). The majority of screening failures were due to not meeting

inclusion criteria of documented CMV infection in whole blood or plasma and not refractory to most recently administered of four anti-CMV treatment agents.

Table 8. Patient Screening and Randomization, Trial 303

Disposition	N
Number of patients screened	415
Number of patients not randomized	63
Number of screening failures	63 of 415 (15%)
Number of patients randomized	352

Source: Figure 2 in the Clinical Study Report.

Patient disposition is shown in Table 9. Note that for patient disposition, subjects who discontinued study drug are not mutually exclusive from subjects who discontinued from the study.

Table 9. Patient Disposition, Trial 303

Disposition Category	Maribavir 400 mg BID N=235 n (%)	IAT N=117 n (%)
Patients randomized	235 (100)	117 (100)
ITT	235 (100)	117 (100)
Per protocol population	223 (95)	108 (92)
Safety population	234 (99.6)	116 (99.1)
Discontinued study drug	51 (22)	79 (68)
Adverse event	15 (6)	36 (31)
Lack of efficacy	21 (9)	16 (14)
Withdrawal by subject	2 (1)	8 (7)
Death	7 (3)	1 (1)
Other	6 (3)[a]	18 (15)[b]
Discontinued study	36 (15)	37 (32)
Adverse event	1 (<1)	5 (4)
Death	24 (10)	8 (7)
Lost to follow-up	2 (1)	1 (1)
Withdrawal by subject	8 (3)	16 (14)
Physician decision	1 (<1)	0
Protocol deviation	0	0
Other[c]	0	7 (6)

Source: Figure 2 of the Clinical Study Report.

[a] Other = Noncompliance, lost to follow-up, PI discretion, PI decision to switch to letermovir (one subject), CMV detected in subject's cerebrospinal fluid (one subject), nothing-by-mouth status with mental status change with risk for aspiration (one subject), and disease progression (one subject).

[b] Other = Noncompliance, lost to follow-up, PI discretion, low viral load/CMV clearance (with concern of toxicity with continued administration of IAT) (9 subjects), subject safety (three subjects), subject/PI request (two subjects), no efficacy and subject ineligible for rescue therapy (one subject), and peripherally inserted central catheter issues (one subject).

[c] Other = Noncompliance, lost to follow-up, no efficacy with IAT for a subject who was not eligible for rescue therapy.

Abbreviations: BID, twice daily; CMV, cytomegalovirus; ITT, intent-to-treat; mITT, modified intention-to-treat; N, number of subjects; n, number of subjects with at least one event; PI, Principal Investigator

Maribavir was observed to be superior to IAT in the primary analysis (56% versus 24%, p<0.001) for the primary efficacy endpoint, confirmed unquantifiable CMV DNAemia (i.e., CMV DNA <LLOQ, i.e., <137 IU/mL), measured at Week 8 (Table 10). For the key secondary endpoint, 19% (44 of 235) of the maribavir subjects responded compared to only 10% (12 of 117) of the subjects randomized to the IAT (p=0.028).

Table 10. Primary and Key Secondary Efficacy Results, Trial 303

CMV Viremia Clearance at Week 8	Maribavir N=235 n (%)	IAT N=117 n (%)
Primary endpoint: CMV DNA <LLOQ at Week 8		
Responders	131 (56)	28 (24)
Adjusted difference in proportion of responders (95% confidence interval)[a]		33 (23, 43)
P-value, adjusted[a]		<0.001
Key secondary endpoint: CMV DNA <LLOQ and CMV infection symptom control at Week 8 with maintenance through Week 16		
Responders	44 (19)	12 (10)
Adjusted difference in proportion of responders (95% confidence interval)[a]		9 (2, 17)
P-value, adjusted[a]		0.02

Source: Statistics Reviewer's Analysis
[a] Mantel-Haenszel weighted average approach was used for the adjusted difference in proportions (maribavir-IAT), the corresponding 95% confidence interval, and the p-value, adjusting for the transplant type and baseline CMV DNA level. Only those with both stratification factors were included in this computation.
Abbreviations: CMV, cytomegalovirus; DNA, deoxyr bonucleic acid; IAT, investigator-assigned treatment; LLOQ, lower limit of quantitation; N, number of subjects in study arm; n, number of subjects within specified category

In Table 11, the main reason for treatment failure in the maribavir arm was virologic non-response, primarily due to CMV DNA never <LLOQ, whereas the main reason for treatment failure in the IAT arm was "Due to drug/ study discontinuation," primarily due to treatment discontinuation or switching treatment due to adverse events. The proportion of virologic non-responders was similar in the IAT and maribavir arms (Table 11) with a higher percentage of subjects in the IAT arm (compared to subjects randomized to maribavir) with CMV DNA never <LLOQ and a higher percentage of subjects in the maribavir arm (compared to subjects randomized to IAT) with CMV DNA breakthrough. Most of the treatment effect favoring maribavir in this table, however, may have been impacted in the IAT arm by the discontinuations (mainly due to adverse events), withdrawal of consent, noncompliance, or other reasons in the IAT arm rather than differences in antiviral activity.

Table 11. Analysis of Failures for the Primary Efficacy Endpoint

Outcome at Week 8	Maribavir N=235 n (%)	IAT N=117 n (%)
Non-responders at Week 8	**104 (44)**	**89 (76)**
Due to virologic failure:	80 (34)	42 (36)
CMV DNA never <LLOQ[a]	48 (20)	35 (30)
CMV DNA breakthrough[b]	32 (14)	7 (6)
Due to drug/study discontinuation:	21 (9)	44 (38)
Adverse events	8 (3)	26 (22)
Deaths	10 (4)	3 (3)
Withdrawal of consent[c]	1 (<1)	9 (8)
Other reasons[c, d]	2 (1)	6 (5)
Other reasons but remained on study[e]	3 (1)	3 (3)

Source: Applicant's Response to information request on September 17, 2021.
[a] LLOQ = 137 IU/mL
[b] CMV DNA breakthrough = achieved viral load <LLOQ and subsequently became detectable.
[c] For subjects who were responding virologically with CMV DNA <LLOQ at the time of drug/study discontinuation. Subjects who were not responding were classified as virologic failures.
[d] Other reasons = other reasons not including adverse events, deaths, noncompliance, and withdrawal of consent, [e] Includes subjects who completed study assigned treatment and were nonresponders.
Abbreviations: CMV, cytomegalovirus; IAT, investigator-assigned treatment; LLOQ, lower limit of quantification; N, number of subjects in study arm; n, number of subjects within specified category

The Applicant's summary of reasons for failure to achieve primary endpoint at Week 8 by treatment group is shown in Table 12. The most common reasons for failure to respond for the primary efficacy endpoint for subjects in the IAT arm were discontinuation of treatment and discontinuation from the study; these included switching to maribavir rescue therapy, switching to prohibited anti-CMV treatment and early discontinuation from the study, each of which occurred in approximately 20% of the randomized subjects. The most common reason for failing to achieve the primary efficacy endpoint in the maribavir arm was CMV DNA measurements through Week 8 not meeting the response criteria, which occurred in 26% of the randomized subjects.

Only 24 (21%) of the 117 subjects randomized to IAT were switched to at least one prohibited anti-CMV treatment, while 22 (19%) of the 117 subjects randomized to IAT were switched to maribavir rescue therapy. Another 21 (18%) of the 117 subjects randomized to IAT discontinued from the study. Therefore, it appears that 57% of the subjects in the IAT treatment arm were not given the opportunity to try other anti-CMV treatments before they were classified as treatment failures as pre-specified for the primary efficacy analysis in the protocol. Note that in addition to treatments to which subjects may have been previously resistant or refractory, such as ganciclovir, valganciclovir, foscarnet, or cidofovir, prohibited switches to anti-CMV treatments also frequently included letermovir. Most subjects were unlikely to have developed resistance or become refractory to letermovir treatment (which, along with the other prohibited anti-CMV treatments, is not approved for treatment of CMV in SOT or HSCT recipients).

The most common reasons for early study discontinuation were withdrawal of consent which occurred in 9% of the 117 subjects in the IAT arm, and death, which occurred in 4% of the randomized subjects in the maribavir arm (Table 12).

Table 12. Reasons for Failure to Achieve Primary Endpoint at Study Week 8 by Treatment Group (Randomized Subjects)

Subject Disposition	Maribavir (N=235) n (%)	IAT (N=117) n (%)
Subjects who achieved primary endpoint	131 (56%)	28 (24%)
Subjects who failed to achieve primary endpoint	104 (44%)	89 (76%)
Reasons for failing to achieve primary endpoint		
CMV measurements through Week 8 but did not meet response criteria	60 (26%)	18 (15%)
Randomized but not dosed and withdrew from the study	1 (<1%)	1 (1%)
Maribavir rescue therapy[a]	0	22 (19%)
Switched to prohibited anti-CMV treatment[b]	26 (11%)	24 (21%)
Missing CMV measurement	17 (7%)	24 (21%)
Due to early discontinuation[c]	16 (7%)	21 (18%)
Death	10 (4%)	3 (3%)
Adverse event	2 (1%)	3 (3%)
Non-compliance with study procedures/visits or study drug	0	4 (3%)
Lack of efficacy	1 (<1%)	0
Withdrawal of consent by subject/parent/guardian	3 (1%)	10 (9%)
Lost to follow-up	0	1 (1%)
Due to other reasons but remained in the study	1 (<1%)	3 (3%)

Source: Table 14.2.1.2 of the Clinical Study Report.
[a] The 22 subjects who switched to maribavir rescue therapy in the IAT arm are not a subset of the 24 subjects who switched to prohibited anti-CMV treatment. Of the 22 IAT subjects who switched to maribavir rescue therapy, 14 switched due to AEs and 8 switched due to lack of efficacy.
[b] Of the 24 IAT subjects who switched to prohibited anti-CMV treatment, 7 switched due to AEs, 6 switched due to lack of efficacy, 2 withdrew from the study, and 9 discontinued treatment due to other reasons. Of the 26 maribavir subjects who switched to prohibited anti-CMV treatment, 5 switched due to AEs, 14 switched due to lack of efficacy, 2 discontinued due to lack of compliance, 2 discontinued treatment due to other reasons and 3 switched due to unknown reasons.
[c] From the Study Completion CRF page or from the End of Treatment CRF page if no reason was given in the Study Completion CRF page.
Abbreviations: AE, adverse event; CRF, clinical report form; CMV, cytomegalovirus; IAT, investigator-assigned treatment; N, number of subjects in treatment arm; n, number of subjects within specified category

The most common reasons for treatment discontinuation among the IAT subjects who switched to maribavir rescue therapy were adverse events followed by lack of efficacy, which occurred in 12% and 7% of the 117 randomized subjects, respectively.

For subjects in the IAT arm, prohibited anti-CMV treatments included addition of, or switch to, another anti-CMV agent or combination therapy with cidofovir and foscarnet. However, withdrawal of one agent was allowed if dual anti-CMV therapy was started for a subject randomized to IAT as were changes in dose and/or dosing regimen. Changes between IV ganciclovir and oral valganciclovir were also allowed.

For subjects randomized to maribavir, reasons for discontinuation of randomized treatment were mostly due to lack of efficacy. Reasons for treatment discontinuation among subjects randomized to IAT who switched to prohibited anti-CMV treatments were mostly due to adverse events, lack of efficacy and other reasons (Table 13).

Table 13. Reasons for Treatment Discontinuation Among Subjects Who Switched to Prohibited Anti-CMV Treatments

Treatment Discontinuation Among Subjects Who Switched Treatment	Maribavir (N=235) n (%)	IAT (N=117) n (%)
Subjects who switched to prohibited anti-CMV treatments	26 (11%)	24 (21%)
Reasons for discontinuing randomized treatment		
Adverse events	5 (2%)	7 (6%)
Lack of efficacy	14 (6%)	6 (5%)
Non-compliance with study schedule	2 (1%)	0
Withdrawal by subject	0	2 (2%)
Other[a]	2 (1%)	9 (8%)
Missing	3 (1%)	0

Source: Statistics Reviewer's analysis.
[a] Other reasons included CMV DNA clearance and prevention of drug toxicity, worsening hemorrhagic cystitis, peripherally inserted central catheter line issues, subjects requesting to be taken of intravenous medications, and patient not doing well with physician decided to end treatment.
Abbreviations: CMV, cytomegalovirus; IAT, investigator-assigned treatment; N, number of subjects in treatment arm; n, number of subjects within specified category

The majority of subjects in the IAT treatment arm took valganciclovir/ganciclovir, or foscarnet. The most common prohibited medications to which subjects (who were originally randomized to the IAT arm) were switched were foscarnet and letermovir. Seventeen percent of IAT subjects switched treatments at least once with the majority of subjects (14%) switching only once (Table 14).

Table 14. Number of Times Subjects Switched to Different Prohibited Anti-CMV Rescue Therapies During the 8-Week Treatment Phase

Number of Subjects With at Least One Treatment Switch	Maribavir (N=234) n (%)	IAT (N=116) n (%)
Number of subjects who switched treatment at least once	27 (12%)	20 (17%)
Exactly once	23 (10%)	14 (12%)
Twice	3 (1%)	5 (4%)
Three or more times	1 (<1%)	1 (1%)

Source: Applicant's table st00397 in their August 9, 2021 response (SDN 018) to an FDA Information Request.
Abbreviations: CMV, cytomegalovirus; IAT, investigator-assigned treatment; MBV, maribavir; N, number of subjects in treatment arm; n, number of subjects within specified category

Subgroup Analyses of the Primary Endpoint

Subgroup analyses demonstrated that efficacy consistently favored maribavir over IAT for age group, including patients ≥65 years of age, gender, race, ethnicity, and transplant type (SOT or HSCT) (Table 15). The proportion of subjects with confirmed CMV DNA <LLOQ at week 8 was significantly higher for both the SOT and HSCT recipients treated with maribavir compared to those treated with IAT.

Subgroup analysis based on baseline CMV DNA levels showed that the higher the CMV DNA levels, the lower the efficacy of maribavir. Virologic response to maribavir decreased significantly with higher CMV DNA levels at baseline. The results were mainly driven by subjects with low CMV DNA levels. These subjects had a response rate of 62% and accounted for 65% of the randomized subjects in the maribavir group.

With regard to the subgroup analysis based on the evidence of genotypic resistance at baseline, the analysis showed that a higher proportion of subjects with evidence of genotypic resistance

who were treated with maribavir had confirmed CMV DNA <LLOQ at Week 8 compared to those treated with IAT (maribavir 63% versus IAT 20%; p<0.001). The difference between the two groups in subjects who were refractory without evidence of genotypic resistance at baseline (refractory) was not statistically significant (maribavir 44% versus IAT 32%; p=0.17), although there was a trend favoring maribavir. There was a statistically significant difference in treatment effects for resistant and refractory subgroups (stratified Breslow-Day p-value=0.028), However, the treatment effect in both the subgroups were going in the same direction and therefore, it can be considered as only a quantitative interaction rather than as a qualitative interaction. Also, the lack of a statistically significant treatment effect in the refractory patients could be due to limited sample size.

In the absence of documented resistance, it is not clear why response rates were lower in the refractory subgroup for maribavir than in the resistant subgroup or in the overall study population unless a host factor (such as level of immune suppression, return of CMV cell-mediated immunity, etc.) also had an important role in CMV DNA undetectability (<LLOQ). In the refractory subgroup, response to maribavir was numerically better than in IAT group, noting, however, that total duration of treatment was longer in maribavir than the IAT arm.

With regards to subjects without CMV syndrome or disease at baseline, subgroup analysis showed that higher proportion of subjects treated with maribavir had CMV DNA <LLOQ at Week 8 compared to those treated with IAT. Subjects with CMV syndrome or disease at baseline responded better with maribavir than subjects treated in the IAT group although the response was not as good as in subjects without CMV syndrome or disease.

Table 15. Subgroup Analysis of the Primary Efficacy Endpoint

Subgroup	Number of Subjects (%) Maribavir 400 mg BID (n=235)	IAT (n=117)	Adjusted Risk Difference (95% CI)	Adjusted p-Value
Age group (years)				
18 to 44	28 of 55 (51%)	8 of 32 (25%)	26% (7%, 46%)	0.008
45 to 64	71 of 126 (56%)	19 of 69 (28%)	30% (16%, 44%)	<0.001
≥65	32 of 54 (59%)	1 of 16 (6%)	54% (33%, 75%)	<0.001
Gender				
Female	44 of 87 (51%)	13 of 52 (25%)	27% (11%, 44%)	<0.001
Male	87 of 148 (59%)	15 of 65 (23%)	36% (23%, 49%)	<0.001
Race				
Black or African American	17 of 29 (59%)	8 of 18 (44%)	9% (-20%, +38%)	0.55
White	100 of 179 (56%)	18 of 87 (21%)	37% (25%, 48%)	<0.001
Asian	5 of 9 (56%)	1 of 7 (14%)	38% (-8%, +84%)	0.11
Other	7 of 16 (44%)	1 of 5 (20%)	23% (-21%, +68%)	0.31
Ethnicity				
Hispanic or Latino	9 of 14 (64%)	1 of 7 (14%)		
Not Hispanic or Latino	107 of 198 (54%)	24 of 95 (25)		
Transplant type				
SOT	79 of 142 (56%)	18 of 69 (26%)	30% (17%, 44%)	<0.001
HSCT	52 of 93 (56%)	10 of 48 (21%)	36% (21%, 51%)	<0.001
Baseline CMV DNA viral load				
Low	95 of 153 (62%)	21 of 85 (25%)	37% (25%, 49%)	<0.001
Intermediate	32 of 68 (47%)	5 of 25 (20%)	26% (6%, 46%)	0.01
High	4 of 14 (29%)	2 of 7 (29%)	5% (-39%, +48%)	0.83
Genotypic resistance to other anti-CMV agents				
Resistant	76 of 121 (63%)	14 of 69 (20%)	44% (31%, 57%)	<0.001
Refractory	42 of 96 (44%)	11 of 34 (32%)	13% (-5%, +31%)	0.17
CMV Syndrome/disease at baseline				
Yes	10 of 21 (48%)	1 of 8 (13%)	30% (-2%, 62%)	0.07
No	121 of 214 (57%)	27 of 109 (25%)	33% (22%, 43%)	<0.001

Source: Statistics reviewer's analysis.
[a] Nominal p-values that are not adjusted for multiple comparisons.
Abbreviations: BID, twice daily; CI, confidence interval; CMV, cytomegalovirus; DNA, deoxyribonucleic acid; IAT, investigator-assigned treatment; SOT, solid organ transplant; HSCT, hematopoietic stem cell transplant

6.2.2. Trial SHP1263-202 (Trial 202)

6.2.2.1. Design, Trial 202

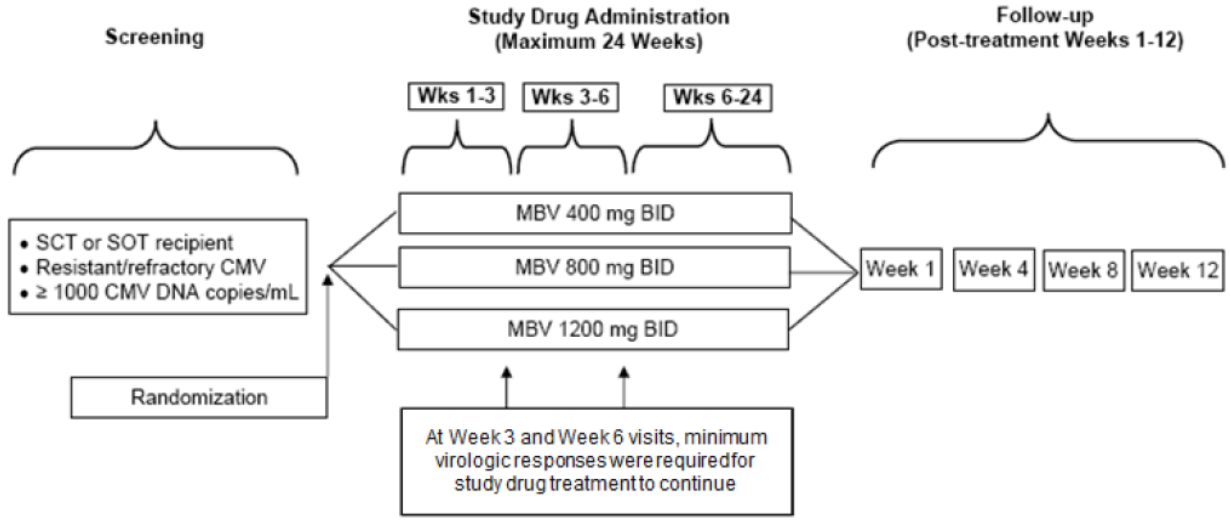
What follows in the summary is taken from the Applicant's CSR unless otherwise specified.

Study 1263-202 was a Phase 2, multicenter, randomized, dose-ranging, parallel-group study of maribavir for the treatment of CMV infections that were resistant or refractory to treatment with ganciclovir/valganciclovir or foscarnet in HSCT or SOT recipients. Subjects who were refractory to treatment were defined as having documented failure to achieve >1 log decrease in CMV DNA level in blood/plasma after an interval of 2 or more weeks of treatment with IV ganciclovir, oral valganciclovir, or IV foscarnet (or any combination thereof). Subjects who were resistant to treatment were defined as being refractory to treatment and having documentation of 1 or more CMV genetic mutations associated with resistance to ganciclovir/valganciclovir and/or foscarnet (Source: p30 of the CSR).

The study was conducted at 27 sites in the United States. Approximately 120 subjects were planned to be randomized in a 1:1:1 allocation ratio to receive oral maribavir at 1 of 3 dose

strengths (400 mg BID, 800 mg BID, or 1,200 mg BID) for up to 24 weeks. Randomization of eligible subjects was stratified by transplant type (HSCT or SOT). All subjects received maribavir, but subjects, investigators, and study staff were blinded to dose strength. During the study, subjects were followed as either inpatients or outpatients, depending on their condition. An overview of the study design is provided in Figure 2.

Figure 2. Study Design Schematic, Trial 202



BID=twice daily; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; MBV=maribavir; SCT=stem cell transplant; SOT=solid organ transplant; Wks=Weeks
Source: Figure 1 in the Clinical Study Report.

Subjects underwent study-specific evaluations on the first day of dosing with study drug (Day 1) and then weekly through Week 6. Safety was assessed by monitoring adverse events (AEs) and changes in physical examinations, vital signs, 12-lead electrocardiograms, and clinical safety laboratory testing (hematology, chemistry, and urinalysis).

Protocol-required CMV monitoring included testing at a central laboratory for the presence of CMV DNA in plasma using polymerase chain reaction. At baseline, a urine sample also was sent to the central laboratory for virus culture testing in an attempt to isolate CMV. Additional CMV testing at local laboratories was performed at the discretion of the Investigator.

Subjects must have achieved at least a minimum virologic response at Weeks 3 and 6 for study drug treatment to continue beyond each of these time points (see Section 5.4.4 CMV Management of the Clinical Study Report for details about the minimum virologic response at Week 3 and 6 required to continue treatment). For subjects who continued dosing after the Week 6 visit, dosing could continue at the discretion of the Investigator through a maximum of 24 weeks in an attempt to decrease CMV DNA to undetectable, and/or to maintain undetectable CMV DNA in an effort to prevent recurrence of CMV infection. Confirmed undetectable CMV was defined as the number of subjects with at least 2 consecutive undetectable plasma CMV DNA results separated by at least 5 days, including early withdrawn qualified subjects. These subjects underwent study-specific evaluations every 2 weeks through Week 12, and again at Weeks 16, 20, and 24.

All subjects who completed study drug treatment or prematurely discontinued study drug for reasons other than withdrawal of consent, lost to follow-up, or AE with an outcome of

death had end- of-treatment procedures performed and underwent follow-up assessments through 12 weeks post-treatment. These included continued CMV testing/assessments, recording of any antiviral therapy used for CMV treatment or prevention, and assessment of survival.

6.2.2.2. Eligibility Criteria, Trial 202

What follows in the summary was taken from the Applicant's CSR unless otherwise specified. Subjects must have:

- Been ≥12 years of age and weighed ≥40 kg.
- Been a recipient of stem cell or solid organ transplantation.
- Had a documented CMV infection in blood or plasma, with a screening value of ≥1,000 DNA copies/mL as determined by qPCR or comparable quantitative CMV assay type.
- Had a current CMV infection that was resistant or refractory to treatment with ganciclovir/valganciclovir or foscarnet.

Subjects must not have:

- Been receiving ganciclovir, valganciclovir, foscarnet, cidofovir*, CMV immune globulin*, leflunomide*, artesunate, or any investigational (unapproved) agent with known anti-CMV activity when study drug was initiated (drugs denoted with * must have been discontinued at least 14 days before the first dose of study drug).
- Had a current CMV infection that was considered resistant or refractory due to inadequate adherence to prior oral anti-CMV treatment.
- Had severe vomiting, diarrhea, or other severe gastrointestinal illness within 24 hours prior to the time of enrollment that would have precluded administration of oral/enteral medication.
- Had severe hepatic impairment, defined as Child-Pugh Class C, based on screening clinical and laboratory assessments.
- Required mechanical ventilation or vasopressors for hemodynamic support at the time of enrollment.
- Expected survival less than 6 weeks.

6.2.2.3. Statistical Analysis Plan, Trial 202

What follows in the summary is taken from the Applicant's CSR unless otherwise specified. The primary efficacy endpoints were:

- Proportion of subjects with confirmed undetectable plasma CMV DNA (central laboratory) within 6 weeks.

Secondary efficacy endpoints included:

- Binary endpoints (yes or no):
  - Proportion of subjects with undetectable plasma CMV DNA (central laboratory) at specified visits.
  - Proportion of subjects with undetectable blood/plasma CMV as assessed by any assay (central or local laboratory) at specified visits.
  - Proportion of subjects with CMV recurrence at any time during the study.
  - Use of any protocol-specified non-study systemic anti-CMV therapies within 6 weeks and at any time during the study.
- Time-to-event endpoints:
  - Time to first confirmed undetectable plasma CMV DNA result (central laboratory) within 6 weeks and at any time during the study.
  - Time to CMV recurrence during the study.
- Numerical endpoints:
  - Change from baseline in plasma CMV DNA (central laboratory) at specified visits.
  - Rate of change in plasma CMV DNA (central laboratory) at Weeks 3 and 6.
  - Number of days in which subjects received any protocol-specified non-study systemic anti-CMV therapies within 6 weeks and at any time during the study.

Point estimates of the treatment effects (overall and by dose group) and 95% confidence intervals (CIs) were provided for dichotomous endpoints. The Kaplan-Meier method was used to estimate the survival functions for time-to-event endpoints using SAS PROC LIFETEST. Kaplan-Meier survival curves for maribavir (overall and by dose group) were provided. Number of events and censoring information were presented in the summary table and the graph of the Kaplan-Meier survival curve.

6.2.2.4. Results of Analyses, Trial 202

The overall percentage of males and females were 57.5% and 42.5% respectively. The median age of the study population was 55 years old and all of the subjects were between 17 and <75 years of age. Approximately 80% of the subjects were white, followed by 10 to 20% who were black/African American. Only 4 to 5% of the subjects in the 400 and 1,200 mg BID doses of maribavir were Hispanic and there were no Hispanics randomized to the 800 mg BID dose. All subjects were from the United States and 80 to 95% of the subjects had no chronic liver disease.

Table 16. Baseline Demographic and Clinical Characteristics, Safety Population, Trial 202

Characteristic	Maribavir 400 mg BID (N=40)	Maribavir 800 mg BID (N=40)	Maribavir 1,200 mg BID (N=40)
Sex, n (%)			
Male	21 (52.5%)	24 (60%)	24 (60%)
Female	19 (47.5%)	16 (40%)	16 (40%)
Age, years			
Mean (SD)	52.1 (14.3)	55.4 (14.1)	50.0 (13.0)
Median (minimum, maximum)	54.5 (18, 74)	61.0 (19, 74)	50.5 (20, 70)

Characteristic	Maribavir 400 mg BID (N=40)	Maribavir 800 mg BID (N=40)	Maribavir 1,200 mg BID (N=40)
Age group (years), n (%)			
≥17 to <65	33 (82.5%)	28 (70.0%)	34 (85.0%)
≥65 to <75	7 (17.5%)	12 (30.0%)	6 (15.0%)
≥75	0 (0.0%)	0 (0%)	0 (0%)
Race, n (%)			
White	32 (80.0%)	31 (77.5%)	32 (80.0%)
Asian	2 (5.0%)	1 (2.5%)	1 (2.5%)
Black/African American	6 (15.0%)	8 (20.0%)	4 (10.0%)
Other	0 (0%)	0 (0%)	3 (7.5%)
Ethnicity, n (%)			
Hispanic	2 (5.0%)	0 (0%)	5 (4.2%%)
Non-Hispanic	37 (92.5%)	40 (100%)	111 (92.5%)
Not reported/unknown	1 (2.5%)	0 (0%)	4 (3.3%)
Country of participation, n (%)			
United States	40 (100%)	40 (100%)	40 (100%)
United Kingdom	0 (0%)	0 (0%)	0 (0%)
Italy	0 (0%)	0 (0%)	0 (0%)
Belgium	0 (0%)	0 (0%)	0 (0%)
Germany	0 (0%)	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)	0 (0%)
Hepatic function, n (%)			
No chronic liver disease	32 (80.0%)	38 (95.0%)	38 (95.0%)
Chronic liver disease			
Child-Pugh Class A	5 (12.5%)	1 (2.5%)	2 (5.0%)
Child-Pugh Class B	3 (7.5%)	1 (2.5%)	0 (0%)
Child-Pugh Class C	0 (0%)	0 (0%)	0 (0%)

Source: Table 7: Subject Demographics from the Clinical Study Report.
Abbreviations: BID, twice daily; N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation

As shown in Table 17, 129 subjects were screened, and of these, 120 were randomized and 9 subjects failed screening. The majority of screening failures (four of nine) did not have documented CMV infections with CMV DNA ≥1,000 copies/mL within 7 days prior to randomization (violation of inclusion criterion #4). Two of nine subjects withdrew from the study. Additional subjects who were screening failures were one subject who did not have a current CMV infection that was resistant or refractory to treatment (violation of inclusion criterion #5), one subject who was receiving a prohibited anti-CMV therapy (violation of exclusion criterion #1), and one subject who had a clinically significant medical or surgical condition that could have interfered with the administration of study drug, interpretation of study results, or compromised the safety or well-being of the subject (violation of exclusion criterion #8).

Table 17. Patient Screening and Randomization, Trial 202

Disposition	Number
Number of patients screened	129
Number of patients not randomized	9
Number of screening failures	9 of 129 (7%)
Number of patients randomized	120

Source: Section 8.1 Disposition of Subjects and Table 11.1.4.1.4.2 in the Clinical Study Report.

Patient disposition for Trial 202 is shown in Table 18. Note that the intent-to-treat population was defined as all randomized subjects. The modified intent-to-treat population was defined as all randomized subjects who received at least one dose of study drug (the Applicant referred to them as the intent-to-treat safety [ITT-S] population). A high proportion (73 to 83%) of subjects discontinued treatment in each arm, mainly due to adverse events, but also due to lack of efficacy or due to efficacy ("recovery from CMV infection"). Note that maribavir dosing could continue up to 24 weeks in this trial in comparison to the 8-week fixed duration of therapy in Trial 303. The differences in dosing duration across trials could account for the higher rates of treatment discontinuation observed in this trial. A similar proportion of subjects discontinued the study in each arm, mainly due to death. The proportion of subjects who died in this trial was higher than that observed in Trial 303, likely due to the longer duration of the study in Trial 202 (up to 24 weeks of treatment with 12 weeks follow-up); whereas in Trial 303, subjects received 8 weeks of treatment and 12 weeks of follow-up.

Table 18. Patient Disposition, Trial 202

Disposition Category	Maribavir 400 mg BID N=40 n (%)	Maribavir 800 mg BID N=40 n (%)	Maribavir 1,200 mg BID N=40 n (%)
Patients randomized	40 (100)	40 (100%)	40 (100%)
ITT/mITT population	40 (100)	40 (100%)	40 (100%)
Per protocol population	31 (78)	33 (83%)	27 (68%)
Safety population	40 (100)	40 (100%)	40 (100%)
Discontinued study drug	31 (78)	33 (83%)	29 (73)
Adverse event	10 (25%)	15 (38%)	14 (35%)
Lack of efficacy	8 (20%)	7 (18%)	6 (15%)
Physician decision	4 (10%)	2 (5%)	2 (5%)
Recovery (from CMV infection)	8 (20%)	9 (23%)	7 (18%)
Withdrawal by subject	1 (3%)	0	0
Discontinued study	15 (38%)	15 (38%)	16 (40%)
Death	10 (25%)	12 (30%)	10 (25%)
Lost to follow-up	0	1 (3%)	0
Withdrawal by subject	0	1 (3%)	4 (10%)
Physician decision	5 (13%)	1 (3%)	2 (5%)
Protocol deviation	0	0	0
Other	0	0	0

Source: Table 6 in the Clinical Study Report.
Abbreviations: BID, twice daily; CMV, cytomegalovirus; ITT, intent-to-treat; mITT, modified intention-to-treat; N, number of subjects in each study arm; n, number of subjects with at least one event

The percentage of subjects who met the primary efficacy endpoint ranged from 62.5% in the maribavir 800 mg BID arm to 70% in the maribavir 400 mg BID arm. There was no apparent dose-response (Table 19). What the Applicant called 'treatment effect' was the proportion of subjects with confirmed undetectable plasma CMV DNA using the total number of subjects in the ITT-S population as the denominator (i.e., subjects with missing data were counted as nonresponders). Clopper-Pearson confidence intervals were computed for the binomial proportions.

Table 19. Primary Efficacy Analysis of Confirmed Undetectable Plasma CMV DNA Within 6 Weeks (Central Laboratory) (ITT-S Population), Trial 202

	Maribavir 400 mg BID N=40	Maribavir 800 mg BID N=40	Maribavir 1200 mg BID N=40	Maribavir All Doses N=120
Subjects with missing data [a], n (%)	0	0	2 (5.0)	2 (1.7)
Subjects with confirmed undetectable plasma CMV DNA, n (%)				
Yes	28 (70.0)	25 (62.5)	27 (67.5)	80 (66.7)
No	12 (30.0)	15 (37.5)	11 (27.5)	38 (31.7)
Treatment effect estimate by group				
Estimated rate [b]	0.70	0.63	0.68	0.67
95% confidence interval [c]	(0.53, 0.83)	(0.46, 0.77)	(0.51, 0.81)	(0.57, 0.75)

BID=twice daily; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; ITT-S=Intent-to-treat Safety
[a] No plasma CMV DNA measurement post-baseline within the assessment period (ie, 6 weeks).
[b] Numerator is the number of "Yes" subjects. Denominator is the number of ITT-S subjects.
[c] Calculated using the exact (Clopper-Pearson) confidence limits for the binomial proportion.
Source: Table 20 of the Clinical Study Report.

6.2.3. Trial SHP1263-203 (Trial 203)

6.2.3.1. Design, Trial 203

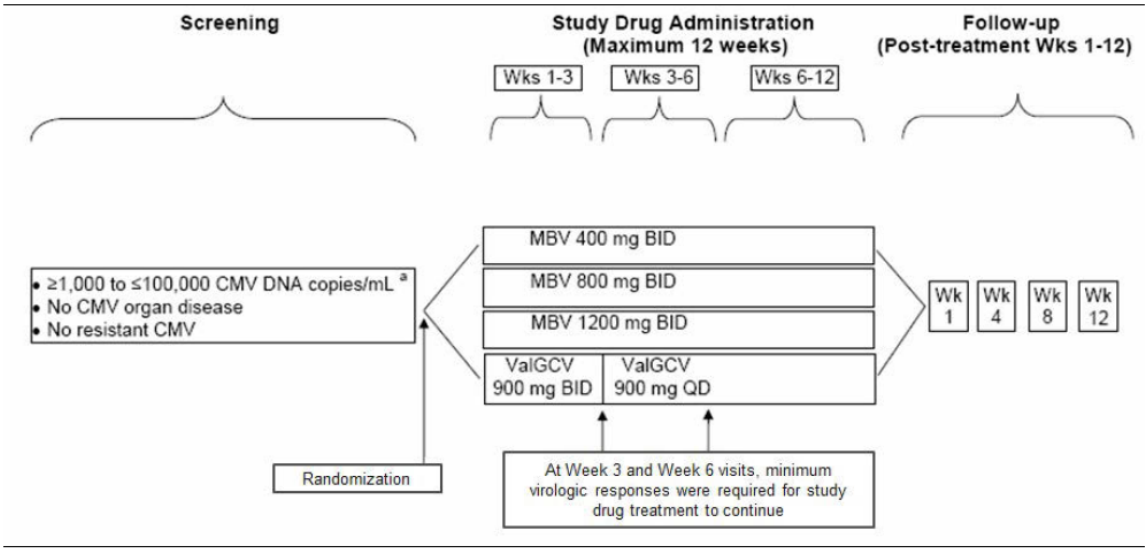
What follows in the summary is taken from the Applicant's CSR unless otherwise specified.

In study 1263-203, subjects were randomized in a 1:1:1:1 allocation ratio to each dose of maribavir and the active control arm (oral valganciclovir), after stratification by transplant type (SOT versus HSCT). The Applicant used the interactive voice and web response system with a central block randomization process based on the transplant type stratification variable. The study targeted having a minimum of 25% of all randomized subjects having baseline CMV DNA of at least 10,000 copies/mL in order to have assess the activity of maribavir in a sufficient number of subjects with high baseline viral loads.

Subjects must have achieved at least a minimum virologic response at Weeks 3 and 6 for study drug treatment to continue beyond each of these time points (see Section 5.4.2 CMV Management of the Clinical Study Report for details about the minimum virologic response at Week 3 and 6 required to continue). For subjects who continued dosing after the Week 6 visit, dosing could continue at the discretion of the Investigator through a maximum of 12 weeks in an attempt to decrease CMV DNA to undetectable levels (<200 copies/mL), and/or to maintain undetectable CMV DNA in an effort to prevent recurrence of CMV infection. These subjects underwent study-specific evaluations every 2 weeks through Week 12.

The design for Trial 203 is shown in Figure 3.

Figure 3. Study Design Schematic, Trial 203



BID=twice daily; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; MBV=maribavir; QD=once daily; ValGCV=valganciclovir; Wk(s)=Week(s)

[a] A target of ~25% of all randomized subjects were to have ≥10,000 CMV DNA copies/mL in plasma at baseline.

Source: Figure 1 in the Clinical Study Report.

6.2.3.2. Eligibility Criteria, Trial 203

What follows in the summary was taken from the Applicant's CSR unless otherwise specified.

Subjects must have:

- Been ≥18 years of age.
- Been a recipient of stem cell or solid organ transplantation.
- Had a documented CMV infection in blood or plasma, with a screening value of ≥1,000 to ≤100,000 DNA copies/mL as determined by qPCR or comparable quantitative CMV assay type. Results from either the central laboratory or a local laboratory could be used for qualification.
- Had a CMV infection that was not known to be resistant to ganciclovir/valganciclovir, foscarnet, or cidofovir based on genotypic evidence (refer to Appendix VIII of the study protocol in Section 16).
- Had all of the following findings as part of screening laboratory assessments (results from either the central laboratory or a local laboratory could be used for qualification):
  - Absolute neutrophil count ≥500/mm^3 (0.5×10^9/L).
  - Platelet count ≥25,000/mm^3 (25×10^9/L).
  - Hemoglobin ≥8 g/dL.
- *If female*, been either postmenopausal, surgically sterile, or had a negative pregnancy test as part of screening laboratory assessments (pregnancy test results from either the central laboratory or a local laboratory could be used for qualification). Women of childbearing potential also must have agreed to use an acceptable method of birth control, as determined by the Investigator, during the study drug administration period and for

3 months afterward. Hormonal contraceptives should not have been used as the sole method of birth control.
- *If male,* agreed to use an acceptable method of birth control, as determined by the Investigator, during the study drug administration period and for 3 months afterward.
- Been able to swallow tablets.
- Been informed of the nature of the study and provided written informed consent before any study-specific procedures were performed. Note: Subjects must have been fully able to give their consent.
- Been assessed by the Investigator to determine whether prophylaxis for non-CMV herpesvirus infections (e.g., herpes simplex virus type 1 and type 2 and varicella zoster virus) was appropriate according to institutional guidelines or standard practices, keeping in mind that maribavir is not active in vitro against these viruses.

6.2.3.3. Statistical Analysis Plan, Trial 203

What follows in the summary is taken from the Applicant's CSR unless otherwise specified.

The primary efficacy endpoints were:

- Confirmed undetectable plasma CMV DNA (central laboratory) within 3 weeks, defined as 2 consecutive post-baseline, on-treatment undetectable results (<200 copies/mL) separated by at least 5 days.
- Confirmed undetectable plasma CMV DNA (central laboratory) within 6 weeks.

Secondary efficacy endpoints included:

- Undetectable plasma CMV DNA (central laboratory) at specified visits.
- Undetectable blood/plasma CMV as assessed by any assay (central or local laboratory) at specified visits.
- Cytomegalovirus recurrence within the study participation period, defined as achievement of undetectable plasma CMV DNA (central laboratory) at any time after Day 1 in at least 2 consecutive samples separated by at least 5 days, followed by detectable plasma CMV DNA (central laboratory) in at least 2 consecutive samples separated by at least 5 days; central laboratory plasma CMV DNA polymerase chain reaction values of ≥200 copies/mL were considered detectable.
- Use of any non-study systemic anti-CMV therapies within 6 weeks, including ganciclovir, valganciclovir, foscarnet, cidofovir, CMV immune globulin (IV CMV immunoglobin, Cytogam®), leflunomide, or artesunate.

All subjects who receive at least one partial or complete dose of study drug, i.e., the ITT-S population, will be included in the analysis of safety. Actual study drug received will be used as the basis for all baseline and safety summaries.

Dichotomous endpoints were summarized using proportions of responders among subjects in the ITT-S population, with exact 95% confidence intervals calculated using the Clopper-Pearson method. Subjects with missing data were assumed to be nonresponders. Risk differences were computed for differences in proportions of subjects with undetectable plasma CMV DNA for each dose of maribavir compared to valganciclovir. The Applicant used odds ratios and the CMH test to compare treatment groups. For consistency with the analyses in study 303 and for further insight, the statistics reviewer compared each dose of maribavir to the active control arm using

risk differences and two-sided Mantel-Haenszel tests stratified by baseline CMV DNA and transplant type.

6.2.3.4. Results of Analyses, Trial 203

The median age of the study population was 58 years old and almost all of the subjects were between 18 and <75 years of age. The majority of subjects in each treatment group were male (55 to 67.5%). The majority of subjects were white (ranging from 80% in the valganciclovir arm to 100% in the 1,200 mg BID maribavir arm), followed by 4% who were Asian and 4% who were black or African American. See Table 20.

Table 20. Baseline Demographic and Clinical Characteristics, ITT-S Population, Trial 203

	Maribavir 400 mg BID (N=40)	Maribavir 800 mg BID (N=40)	Maribavir 1200 mg BID (N=39)	Maribavir All Doses (N=119)	Valganciclovir 900 mg BID (N=40)
Age (years)					
Mean (SD)	53.0 (14.18)	54.4 (12.72)	55.9 (10.69)	54.4 (12.57)	54.5 (12.36)
Median (min, max)	56.5 (29, 76)	58.5 (18, 74)	58.0 (25, 74)	58.0 (18, 76)	58.5 (28, 76)
Distribution of age (years), n (%)					
18 to 44	11 (27.5)	7 (17.5)	5 (12.8)	23 (19.3)	9 (22.5)
45 to 64	16 (40.0)	26 (65.0)	26 (66.7)	68 (57.1)	24 (60.0)
65 to 75	12 (30.0)	7 (17.5)	8 (20.5)	27 (22.7)	6 (15.0)
>75	1 (2.5)	0	0	1 (0.8)	1 (2.5)
Gender, n (%)					
Female	18 (45.0)	13 (32.5)	17 (43.6)	48 (40.3)	13 (32.5)
Male	22 (55.0)	27 (67.5)	22 (56.4)	71 (59.7)	27 (67.5)
Weight (kilograms)					
Female, N	17	13	17	47	13
Mean (SD)	72.1 (14.65)	62.1 (14.83)	58.0 (14.43)	64.2 (15.59)	62.5 (11.88)
Median (min, max)	71.5 (43.0, 98.0)	60.0 (39.1, 97.0)	56.6 (39.5, 106.5)	61.0 (39.1, 106.5)	66.3 (41.0, 77.6)
Male, N	22	27	22	71	27
Mean (SD)	73.5 (10.14)	76.7 (12.90)	72.8 (14.27)	74.5 (12.53)	76.1 (14.22)
Median (min, max)	71.5 (54.2, 98.0)	74.9 (44.0, 105.8)	71.3 (51.0, 117.0)	73.5 (44.0, 117.0)	74.0 (52.2, 111.3)
Race, n (%)					
Asian	2 (5.0)	1 (2.5)	0	3 (2.5)	4 (10.0)
Black or African American	1 (2.5)	2 (5.0)	0	3 (2.5)	3 (7.5)
White	37 (92.5)	37 (92.5)	39 (100.0)	113 (95.0)	32 (80.0)
Other	0	0	0	0	1 (2.5) [a]
Ethnicity, n (%)					
Hispanic or Latino	5 (12.5)	4 (10.0)	4 (10.3)	13 (10.9)	8 (20.0)
Not Hispanic or Latino	35 (87.5)	34 (85.0)	35 (89.7)	104 (87.4)	31 (77.5)
Not Reported/Unknown	0	2 (5.0)	0	2 (1.7)	1 (2.5)

Source: Table 7 in the Clinical Study Report.
[a] Moroccan.
Percentages are based on the number of subjects in each treatment group (ITT-S population).
Abbreviations: BID, twice daily; ITT-S, intent-to-treat-safety; max, maximum; min, minimum; N, number of subjects in study arm; SD, standard deviation

A total of 13 of 174 subjects were screening failures (Table 21). The majority of screening failures (10 of 13) did not have documented CMV infections with CMV DNA ≥1,000 to ≤100,000 copies/mL (violation of inclusion criterion #3), followed by 2 of 13 subjects who withdrew consent. An additional subject was enrolled in another (non-CMV) investigational study (Investigator-determined violation of exclusion criterion #9).

Table 21. Patient Screening and Randomization, Trial 203

Disposition	Number
Number of patients screened	174
Number of patients not randomized	13
Number of screening failures	13 of 174 (7%)
Number of patients randomized	161

Source: Section 8.1 Disposition of Subjects and Table 11.1.4.1.4.2 in the Clinical Study Report.

Patient disposition for Trial 203 is shown in Table 22. Forty subjects were randomized to each maribavir arm (400 mg BID, 800 mg BID, and 1,200 mg BID), and 41 subjects were randomized to the valganciclovir arm (900 mg BID). After the first 3 weeks of treatment valganciclovir dose was reduced to 900 mg daily. The percentage of subjects discontinuing treatment was 65 to 80% in maribavir subjects and 66% in valganciclovir subjects. The most common reason for not completing treatment or for discontinuing study drug before the protocol-specified maximum treatment duration of 12 weeks, was "recovery from CMV infection" as judged by the Investigator (maribavir, 30 to 55%; valganciclovir, 34%). As noted for Trial 202, the most likely explanation for the increased rates of treatment discontinuation in this trial in comparison to Trial 303, is the longer duration of therapy in this trial (12 weeks treatment, followed by 12 weeks of follow-up). The second most common reason for not completing treatment was adverse events (maribavir, 13 to 25%; valganciclovir, 15%) while the third most common reason was lack of efficacy (maribavir, 5 to 10%; valganciclovir, 7%).

The percentage of subjects discontinuing the study was 10 to 13% in maribavir subjects and 15% in valganciclovir subjects. The most common reason for not completing the study was death (3 to 8% in maribavir subjects; 8% in valganciclovir subjects). The second most common reason was withdrawal by subject (0 to 8% in maribavir subjects; 7% in valganciclovir subjects).

Table 22. Patient Disposition, Trial 203

Disposition Category	Maribavir 400 mg BID N=40 n (%)	Maribavir 800 mg BID N=40 n (%)	Maribavir 1,200 mg BID N=40 n (%)	Valganciclovir 900 mg BID N=41 n (%)
Patients randomized	40 (100)	40 (100)	40 (100)	41 (100)
ITT population	40 (100)	40 (100)	40 (100)	40 (100)
Per protocol population	32 (80)	34 (85)	29 (73)	32 (78)
Safety population	40 (100)	40 (100)	39 (98)	40 (98)
Discontinued study drug	27 (68)	32 (80)	26 (65)	27 (66)
Adverse event	8 (20)	5 (13)	10 (25)	6 (15)
Lack of efficacy	4 (10)	2 (5)	2 (5)	3 (7)
Physician decision	1 (3)	0	0	2 (5)
Recovery (from CMV infection)	13 (33)	22 (55)	12 (30)	14 (34)
Sponsor decision	0	1 (3)	0	0
Withdrawal by subject	1 (3)	2 (5)	2 (5)	2 (5)
Discontinued study	4 (10)	4 (10)	5 (13)	6 (15)
Death	1 (3)	1 (3)	3 (8)	3 (8)
Lost to follow-up	2 (5)	0	0	0
Withdrawal by subject	0	3 (8)	2 (5)	3 (7)
Physician decision	1 (3)	0	0	0
Protocol deviation	0	0	0	0
Other	0	0	0	0

Source: Tables 5 and 6 of the Clinical Study Report.
Abbreviations: BID, twice daily; CMV, cytomegalovirus; ITT, intention-to-treat; N, number of subjects; n, number of subjects with at least one event

Trial 203 results are shown in Table 23 and Table 24, using odds ratio (Table 23) and risk difference (Table 24). At week 3, 58 to 65% subjects treated with maribavir and 55% of those treated with valganciclovir had undetectable CMV DNA; while at Week 6, the proportion of subjects with undetectable CMV DNA increased for both maribavir and valganciclovir groups (72% to 83% for maribavir and 65% in those treated with valganciclovir). No dose-response was observed across the maribavir doses used in this trial and none of the treatment comparisons with the control were statistically significant.

Table 23. Analysis of Confirmed Undetectable Plasma CMV DNA (Central Laboratory) Within 3 and 6 Weeks (ITT-S Population), Trial 203

	Maribavir 400 mg BID (N=40)	Maribavir 800 mg BID (N=40)	Maribavir 1200 mg BID (N=39)	Maribavir All Doses (N=119)	Valganciclovir 900 mg BID (N=40)
Week 3					
Subjects with missing data [a], n (%)	1 (2.5)	0	1 (2.6)	2 (1.7)	1 (2.5)
Subjects with undetectable plasma CMV DNA, n (%)					
Yes	26 (65.0)	23 (57.5)	23 (59.0)	72 (60.5)	22 (55.0)
No	13 (32.5)	17 (42.5)	15 (38.5)	45 (37.8)	17 (42.5)
Treatment effect estimate by group					
Estimated rate [b]	0.67	0.58	0.61	0.62	0.56
95% CI	(0.50, 0.81)	(0.41, 0.73)	(0.43, 0.76)	(0.52, 0.70)	(0.40, 0.72)
Treatment comparison with control [c]					
Odds ratio	1.79	1.20	1.27	1.42	
95% CI for the odds ratio	(0.63, 5.08)	(0.44, 3.22)	(0.46, 3.53)	(0.62, 3.24)	
p-value	0.2775	0.7218	0.6437	0.4107	
Week 6					
Subjects with missing data [a], n (%)	1 (2.5)	0	1 (2.6)	2 (1.7)	1 (2.5)
Subjects with undetectable plasma CMV DNA, n (%)					
Yes	31 (77.5)	33 (82.5)	28 (71.8)	92 (77.3)	26 (65.0)
No	8 (20.0)	7 (17.5)	10 (25.6)	25 (21.0)	13 (32.5)
Treatment effect estimate by group					
Estimated rate [b]	0.79	0.83	0.74	0.79	0.67
95% CI	(0.64, 0.91)	(0.67, 0.93)	(0.57, 0.87)	(0.70, 0.86)	(0.50, 0.81)
Treatment comparison with control [c]					
Odds ratio	2.13	2.97	1.48	2.12	
95% CI for the odds ratio	(0.72, 6.30)	(0.94, 9.35)	(0.53, 4.16)	(0.91, 4.96)	
p-value	0.1712	0.0633	0.4528	0.0822	

BID=twice daily; CI=confidence interval; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; ITT-S=Intent-to-treat Safety

[a] No plasma CMV DNA measurement post-baseline within the assessment period (i.e., 3 weeks or 6 weeks).

[b] Numerator is the number of "Yes" subjects; denominator is the number of ITT-S subjects with non-missing data.

[c] Logistic regression model for maribavir vs. valganciclovir (SAS PROC LOGISTIC): y = treatment + baseline plasma CMV DNA + transplant type.

Source: Table 20 in the Clinical Study Report.

Risk differences were computed for differences in proportions of subjects with undetectable plasma CMV DNA (for each dose of maribavir to valganciclovir) at Week 6 and were compared

using the two-sided Mantel-Haenszel test stratified by baseline CMV DNA (Low, Intermediate/High) and transplant type (SOT or HSCT). None of these risk differences comparing each dose of maribavir and all doses of maribavir combined against valganciclovir were statistically significant.

Table 24. Efficacy Risk Differences at Week 6, Trial 203

Week 6 Maribavir Comparison With Valganciclovir	Maribavir 400 mg BID (N=39)	Maribavir 800 mg BID (N=40)	Maribavir 1,200 mg BID (N=38)	Maribavir All Doses (N=117)
Risk difference	0.14	0.18	0.04	0.13
95% CI for risk difference	-0.03, +0.31	-0.00, +0.36	-0.15, +0.23	-0.02, +0.28
Two-sided p-value[a]	0.11	0.052	0.66	0.10

Source: Statistics Reviewer's analysis.
[a] Two-sided Mantel-Haenszel test stratified by baseline CMV DNA and transplant type, comparing each dose of maribavir and all doses combined to valganciclovir.
Abbreviations: BID, twice daily; CI, confidence interval; N, number of subjects in study arm

Additional analyses of the number of subjects with CMV recurrence within the first 6 weeks, number of subjects with CMV recurrence within the study participation period, use of any non-study systemic anti-CMV therapies after Day 1 and within 6 weeks and time to confirmed undetectable plasma CMV DNA (central laboratory) within 6 weeks are shown in Section III.16.

6.3. Key Review Issues Relevant to Evaluation of Benefit

6.3.1.1. Does the Phase 3 Trial, SHP620-303, Provide Substantial Evidence of Effectiveness for Treatment of Resistant CMV Infection/Disease?

Issue

The single Phase 3 trial, SHP1263-303, was open-label leading to *potential selection bias* by allowing the study subjects and investigators to selectively switch treatment arms or discontinue from the trial knowing what treatments subjects were taking.

Background

This trial was a Phase 3, multicenter, randomized, open-label, active-controlled study to assess the efficacy and safety of maribavir compared to the IAT in HSCT and SOT recipients with CMV infections that were resistant/refractory to treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir. The subject enrollment was monitored to achieve an approximate target of 60% of subjects with documented resistance. While subjects had to be refractory with or without genotypic resistance to at least 1 of these anti-CMV agents to be eligible for the study per the protocol definition, the Principal Investigator individualized the IAT for subjects randomized to the IAT arm, selecting 1 or 2 of the 4 available anti-CMV agents with knowledge of a subject's past medical history and clinical course with treatment of the current CMV infection and after considering the risk/benefit of potential treatment options for the subject (i.e., the best available therapy). Thus, the IAT arm consisted of a heterogeneous population of subjects. All eligible subjects were stratified by transplant type (HSCT and SOT) and by the most recent screening CMV DNA viral load. Following stratification, subjects were randomized

in a 2:1 allocation ratio to receive open-label maribavir 400 mg BID or IAT (ganciclovir, valganciclovir, foscarnet, or cidofovir) for 8 weeks. Subjects in the IAT arm could stop treatment at the discretion of the Investigator for lack of confirmed CMV DNA <LLOQ and/or intolerance to the assigned treatment. Only subjects with clear evidence of virologic failure with or without clinical failure (i.e., no improvement or progression of CMV disease, rather than merely for intolerance to IAT) after a minimum of 3 weeks of treatment could be evaluated by the medical monitor for entry into the rescue arm, starting at Visit 5/Week 3. Rescue treatment was with maribavir 400 mg BID for 8 weeks.

For inclusion in the trial, subjects had to have a documented CMV infection in whole blood or plasma, with a screening value of ≥2,730 IU/mL in whole blood or ≥910 IU/mL in plasma in 2 consecutive assessments, separated by at least 1 day, as determined by local or central specialty laboratory qPCR or comparable quantitative CMV DNA results. Both samples should have been taken within 14 days prior to randomization with second sample obtained within 5 days prior to randomization. The same laboratory and same sample type (whole blood or plasma) should have been used for these assessments. The subject had to have a current CMV infection that was resistant/refractory to the most recently administered of the 4 anti-CMV treatment agents.

Refractory was defined as documented failure to achieve >1 $\log_{10}$ IU/mL decrease in CMV DNA level in whole blood or plasma after a 14-day or longer treatment period with IV ganciclovir/oral valganciclovir, IV foscarnet, or IV cidofovir. Resistant subjects had documentation of 1 or more amino acid substitutions associated with resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir and also met the definition of refractory HCMV infection. The central laboratory used the FDA-approved COBAS® AmpliPrep/COBAS® TaqMan® CMV Test (CAP/CTM) (Roche 2017) while qualified local laboratories could use any quantitative polymerase chain reaction or comparable quantitative CMV deoxyribonucleic acid (DNA) test. Randomized subjects had a baseline CMV viral load performed immediately prior to the start of treatment. CMV DNA quantification for the baseline and all subsequent on-study samples was performed at the central specialty laboratory using the COBAS AmpliPrep/COBAS TaqMan CMV assay according to the study schedule of assessments. Additional CMV DNA tests at local laboratories were performed and collected at the discretion of the Investigator.

The antiviral activity of maribavir is mediated by competitive inhibition of the protein kinase activity of HCMV enzyme pUL97, which results in inhibition of the phosphorylation of proteins. Of note, the resistant population is a subset of the refractory population (phenotypic resistance). Subjects who were refractory, i.e., phenotypically resistant, may not have been identified as "resistant" as they may have had a yet to be identified valganciclovir/ganciclovir resistance-associated substitution(s).

The primary efficacy endpoint was confirmed unquantifiable CMV DNAemia (defined as plasma CMV DNA concentration below the lower limit of quantification (LLOQ i.e., <137 IU/mL)) as assessed by COBAS AmpliPrep/COBAS TaqMan CMV assay following 8 weeks of therapy.

Because this trial was open-label, treatments were known to the Investigator and the subject. If a subject experienced an adverse event in the IAT arm, study drug may have been discontinued or subject switched to prohibited therapy whether or not subject was responding to the IAT. Such discontinuations and switches were considered failures in the primary analysis. If the Investigator and subject were blinded to treatment arm, such discontinuations and switches may

have been less likely to occur in the IAT arm. In this trial, the most common reason for treatment failure in the IAT arm was treatment discontinuation or switch due to an AE, and thus results could potentially be biased in favor or maribavir.

Assessment

Primary Efficacy Analysis

Maribavir was observed to be superior to IAT in the primary analysis (56% versus 24%, p<0.001) for the primary efficacy endpoint, confirmed unquantifiable CMV DNA <LLOQ (i.e., <137 IU/mL), measured at week 8, as shown in Table 10. Notably, the main reason for treatment failure in the maribavir arm was virologic failure, primarily due to CMV DNA never achieving <LLOQ, while the main reason for treatment failure in the IAT arm was missing data at week 8, primarily due to treatment discontinuation or switching treatment due to adverse events (Table 11). The overall proportion of virologic failures was similar between the arms, but a higher proportion of subjects in the IAT arm than in the maribavir arm failed to achieve CMV DNAemia <LLOQ, while more subjects in the maribavir arm than IAT arm achieved CMV DNA <LLOQ and then experienced CMV DNA breakthrough.

Key Secondary Endpoints

The key secondary endpoint, maintenance of CMV DNA <LLOQ through week 16 and control of CMV symptoms (in those with CMV disease), demonstrated statistical superiority of maribavir over IAT and supported the primary endpoint (Table 10). However, the key secondary efficacy endpoint at Week 16 required that subjects responded at Week 8. Therefore, any selection bias that potentially lowered the response rate for the primary efficacy analysis at Week 8 could also have led to lower response rates later on at Week 16.

Sensitivity Analyses of the Primary Efficacy Endpoint

These sensitivity analyses were conducted to examine the effect of potential bias in Trial 303.

Maribavir was superior to IAT in the sensitivity analysis for the primary efficacy endpoint (60% versus 44%, p<0.001) when subjects who had CMV DNA <LLOQ at the time of early study discontinuation were also counted as responders (i.e., when the last observation carried forward [LOCF] imputation was used for both treatment groups). See Table 25.

In addition, maribavir was observed to be superior to IAT in the sensitivity analysis for the primary efficacy endpoint at Week 8 (59% versus 43%, p=0.001). Response was based on CMV DNA levels regardless of alternative anti-CMV or rescue treatment for both treatment groups. See Table 25.

Table 25. Sensitivity Analyses of the Primary Efficacy Endpoint Based on Alternate Definitions of Response (Randomized Patients)

Analysis	Maribavir 400 mg BID (N=235)	IAT (N=117)	Risk Difference (95% CI)	Adjusted p-Value
Definition 1				
Responders[a, b], n (%)	141 (60%)	51 (44%)	18% (7%, 29%)	0.001
Definition 2				
Responders[a], n (%)	139 (59%)	50 (43%)	18% (7%, 28%)	0.001

Source: Statistics Reviewer's analysis.
Definition 1: Included subjects who met the criteria of confirmed CMV viremia clearance at the time of early discontinuation as a responder (LOCF imputation)
Definition 2: Included subjects who met the criteria of confirmed CMV viremia clearance at Week 8 based on CMV DNA levels regardless of prohibited anti-CMV treatment or maribavir rescue therapy as a responder (PENDPT4B[a])
[a] Response was assessed regardless of whether the study randomized treatment was discontinued before the end of the stipulated 8 weeks of therapy.
[b] Plasma CMV DNA assessments after starting prohibited anti-CMV treatment or maribavir rescue therapy were not evaluable for the assessment of response.
Abbreviations: BID, twice daily; CI, confidence interval; CMV, cytomegalovirus; IAT, investigator-assigned treatment; LOCF, last observation carried forward; N, number of subjects in study arm; n, number of subjects within specified category

In an attempt to examine the effect of open-label bias where subjects may have dropped out early after finding out they were not receiving maribavir, additional sensitivity analyses excluded subjects who discontinued after only 72 hours, 7, 14, 21, and 28 days. These analysis exclude subjects who may have discontinued IAT early after subjects or investigators learned they were not receiving maribavir. Statistically significant results favoring maribavir over the IAT were still observed in each of these analyses. For further details, see Table 120.

Subgroup Analyses

As detailed in Section 6.2.1.4, most subgroup analyses favored maribavir over IAT, and the majority of analyses showed statistical significance with the exception of black/African American race, refractory CMV without genotypic resistance, and presence of CMV syndrome or CMV tissue invasive disease. Trial 303 was not powered for any of the subgroup analyses.

Some additional subgroup analyses were performed as post hoc analyses by the statistical reviewer to explore whether open-label bias could have been a factor in study outcome, as described below.

One of the issues with the trial design was switching from either arm to prohibited anti-CMV therapy and switching in the IAT arm to maribavir rescue therapy. A total of 24 (21%) of the 117 subjects randomized to IAT were switched to at least one prohibited anti-CMV treatment, while 22 (19%) of the 117 subjects randomized to IAT were switched to maribavir rescue therapy. Another 21 (18%) of the 117 subjects randomized to IAT discontinued from the study (Table 12). Therefore, it appears that 58% of the subjects in the IAT treatment arm were not given the opportunity to try other anti-CMV treatments before they were classified as treatment failures as pre-specified for the primary efficacy analysis in the protocol. Note that in addition to treatments to which subjects may have been previously resistant or refractory, such as ganciclovir, valganciclovir, foscarnet, or cidofovir, prohibited switches to anti-CMV treatments also frequently included letermovir. Most subjects were unlikely to have developed resistance or become refractory to letermovir treatment (which, along with the other prohibited anti-CMV treatments, is not approved for treatment of CMV in SOT or HSCT recipients).

Among the subjects who switched treatments, the percentage of subjects who met the primary efficacy endpoint by responding at Week 8 ranged from 27% for subjects randomized to

maribavir who switched to prohibited anti-CMV treatment to 46% in subjects randomized to IAT who switched to prohibited anti-CMV treatment (Table 26). This suggests that efficacy in the IAT arm in the primary analysis could have been better than what was observed in this trial had other anti-CMV drugs not been prohibited, although the numbers in this analysis are very small. In addition, subjects on IAT appeared to have had their treatment discontinued or switched proportionately more often than subjects on the maribavir arm, possibly due to open-label bias or a flawed study design. If subjects randomized to IAT were allowed to continue on other anti-CMV treatments, then some of these subjects could have responded.

Table 26. Subgroup Analysis of Week 8 Responders Among Subjects Who Switched Treatments

Maribavir → Prohibited Anti-CMV Treatment n=26	IAT→ Prohibited Anti-CMV Treatment n=24	IAT → Maribavir Rescue Therapy[a] n=22
7 (26.9%)	11 (45.8%)	8 (36.4%)[b]

Source: Statistics Reviewer's analysis.
[a] Note that subjects who switched to maribavir rescue therapy were treated with maribavir for up to 8 weeks.
[b] 11 (50%) of the 22 subjects who switched to maribavir rescue therapy responded after 8 weeks of maribavir treatment (see pp.16 and 283 of the Clinical Study Report).
Abbreviations: CMV, cytomegalovirus; IAT, investigator-assigned treatment

Only 37 of the 117 subjects in the IAT arm and 183 of 235 subjects randomized to maribavir completed the full 8 weeks of treatment. In a subgroup analysis for these subjects, the percentage of responders increased substantially for the subjects in the IAT arm and also increased in maribavir subjects compared to response rates in all randomized subjects. The risk difference between maribavir and IAT subjects was only 10% and was not statistically significant, although the trend still favored maribavir subjects compared to active controls, as in Table 27. However, a completers analysis should be interpreted with caution because subjects who complete the trial may be very different from subjects who discontinue early.

Table 27. Subgroup Analyses of the Primary Efficacy Endpoint: Confirmed CMV Viremia Clearance in Subgroup of Subjects Who Received 8 Weeks of Study-Assigned Treatment (Randomized Patients)

Parameter	Maribavir 400 mg BID (N=235)	IAT (N=117)	Risk Difference (95% CI)	Adjusted p-Value
Week 8 Completers, n (%)	183 (78%)	37 (32%)		
Responders[a], n (% of completers)	129 (70%)	22 (59%)	10% (-7%, 27%)	0.242

Source: Statistics Reviewer's analysis.
[a] Plasma CMV DNA assessments after starting proh bited anti-CMV treatment or mar bavir rescue therapy were not evaluable for the assessment of response.
Abbreviations: BID, twice daily; CI, confidence interval; CMV, cytomegalovirus; IAT, investigator-assigned treatment; N, number of subjects in each study arm; n, number of subjects within specified category

Conclusion

In the single Phase 3 trial, the primary efficacy endpoint was met for maribavir, which was shown to be statistically superior to IAT for the primary endpoint. However, the treatment effect appeared to be driven primarily by discontinuation or switching of treatment in the IAT arm due to adverse events, rather than to virologic failure. This result is not unexpected, given that ganciclovir, valganciclovir, foscarnet, and cidofovir have a number of significant toxicities and these drugs, particularly foscarnet and cidofovir, may not be well tolerated for more than a short period of time.

The majority of sensitivity analyses performed by the Applicant (and confirmed by statistical reviewer) supported the primary endpoint analysis, i.e., statistical superiority of maribavir versus IAT for the primary endpoint. However, not all of the sensitivity analyses [e.g., Week 8 completers analysis and Week 8 completers analysis with subsequent recurrences treated as non-responders (see Section III.16)] showed a robust statistically significant treatment effect in favor of maribavir compared to the IAT.

Subgroup analyses generally supported the primary endpoint in the overall population, favoring maribavir over IAT except in the subgroup of subjects with refractory CMV (without genotypic resistance) and in Blacks/African Americans; however, some exploratory subgroup analyses were performed to examine the effects of open-label bias.

Subjects in the IAT arm may not have had the opportunity to try alternative anti-CMV drugs to which they weren't resistant or refractory. A possible design flaw in this trial was that changes to other anti-CMV drugs were not allowed. See Section 5.2.2 of the protocol, which states that "change to another anti-CMV agent during the study treatment period is not allowed (except for change from valganciclovir to ganciclovir, or vice versa)." In addition, investigators and/or subjects may have decided to discontinue IAT prematurely due to the open-label design and resulting potential for selection bias.

Although the incidence of AEs were at least as high in the maribavir arm as in the IAT arm, a higher percentage of subjects in the IAT arm discontinued treatment due to AEs and other reasons than subjects in the maribavir group. Although the percentage of serious AEs was observed to be similar in the two treatment groups, subjects in the maribavir arm were treated for a longer period of time than those in the IAT arm so the percentage of serious AEs may have been underestimated in the IAT arm compared to the maribavir arm. However, open-label selection bias was still a possible explanation why a higher percentage of serious AEs were attributed to the drugs in the IAT group compared to subjects in the maribavir group and why the percentage of subjects who discontinued due to serious AEs was also higher in the IAT arm than in the maribavir arm.

The Phase 3 trial design was open-label because it was not feasible to make the study double-blind due to intravenous treatments in the IAT arm, and due to well-known toxicities associated with each of the drugs which could be used in the IAT arm (e.g., renal impairment and electrolyte abnormalities with foscarnet, and hematologic toxicities with (val)ganciclovir. Additionally, for the IAT arm, investigators had to determine best available therapy for each subject based on resistance genotype. Oral maribavir is difficult to mask due to the taste disturbances associated with its use, and is another reason that trial could not be conducted in a double-blinded manner.

The higher discontinuation rates in the IAT arm compared to the maribavir arm and low percentage of alternative anti-CMV drugs used for treating the active controls that led to lower response rates in the active controls could have been influenced by selection bias. However, the higher rates of discontinuation in the IAT arm were largely due to adverse events, which is not unexpected given the available treatment options in that arm, namely ganciclovir and valganciclovir which are associated with significant hematologic toxicity, foscarnet, which is associated with renal toxicity, severe electrolyte abnormalities, seizures, and many other adverse reactions. Similarly, cidofovir is associated with renal toxicity. The latter two drugs, in particular, are not tolerated for long periods of time without the need for discontinuation.

For a comparative trial to be performed in this population, blinding was not feasible for reasons previously stated. The Advisory Committee was in agreement with this premise and found the evidence of maribavir efficacy in this population acceptable even though its superiority may have been driven mainly by superior tolerability.

Statistical Reviewer's Perspective

The Statistics Reviewer believes that it would have been preferrable to have waited for results from the Phase 3 non-inferiority treatment trial (1263-302) in non-refractory, non-resistant subjects before making a decision to approve this product for the following reasons:

1) the potential design flaws and/or open-label selection bias of trial 303
2) the failure of two well-designed, double-blind Phase 3 prophylaxis trials
3) the fact that the Applicant has never shown that the 400 mg BID dose was better than the 100 mg BID dose used in the phase 3 prophylaxis trials
4) the shortcomings in the two Phase two treatment trials discussed in 6.3.1.3 (b) (4).

One possible explanation for the failure of the two phase 3 prophylaxis trials was that the 100mg BID dose was too low. However, it was never shown that the 400 mg BID dose was better than the 100 mg BID dose in the randomized, double-blind, placebo-controlled, dose-ranging, phase 2 prophylaxis trial (1263-200) to assess the safety, tolerability, and prophylactic anti-cytomegalovirus activity of maribavir in recipients of allogenic stem cell transplants.

Another explanation provided by the Applicant was that the incidence of CMV disease was too low and that the resulting low power explained why the two Phase 3 prophylaxis trials failed. The Applicant stated that CMV disease was not used as a primary endpoint for more recent approvals of drugs like letermovir. This argument is not convincing because there was much higher incidence of CMV infection (33 to 64%) observed using the CMV DNA polymerase chain reaction assay and there was also no statistically significant difference favoring maribavir for this endpoint in either prophylaxis trial (maribavir was statistically significantly worse than ganciclovir in Trial 1263-301 for this endpoint).

Clinical and Virology Reviewer's Perspectives

We note that the prophylaxis population studied in the Phase 3 prophylaxis trials, is a very different population than the population studied in Trial 303, which included subjects with CMV infection or disease who had been treated previously with one or more anti-CMV medications and were refractory to treatment with or without genotypic resistance. Results from the prophylaxis trials are not generally used to support treatment trials, although the opposite may be the case. In the setting of prophylaxis, there is no infection or disease, and antiviral activity can only be directly observed in treatment trials. In addition, the prophylaxis trials used a 4-fold lower dose of maribavir, 100 mg twice daily. Although it is not clear why the maribavir prophylaxis trials failed, data from those trials should not be used to dispute the results from Trial 303.

Further, the ongoing trial, 302, is also evaluating maribavir in a different population, i.e., post-transplant subjects with their first episode of asymptomatic CMV viremia, which is not refractory (with or without genotypic resistance) to ganciclovir, valganciclovir, foscarnet, or cidofovir. Thus, whether data from this trial, could have been used to support the indication for treatment of resistant/refractory CMV infection/disease is not clear at this time.

Although the Clinical reviewer initially agreed with the Statistical reviewer that it would have been preferable to have data from the ongoing trial, 302, for review with this NDA prior to taking regulatory action, after the Advisory Committee discussion and unanimous vote recommending approval, he agreed that maribavir could be approved at this time for a limited indication and population, i.e. treatment of post-transplant CMV refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, foscarnet, or cidofovir. Overall, the Clinical and Virology reviewers and cross-disciplinary team leader concur with the Advisory Committee and agree that the Phase 3 trial, 303, despite its limitations, and the totality of the data in this population, support the proposed indication for treatment of resistant CMV (see Section 6.3.1.2 for discussion of refractory CMV). See also Sections 6.3.1.1 and 6.3.1.3.

The signatory concurs with the perspective.

6.3.1.2. Does the Phase 3 Trial, SHP620-303, Provide Substantial Evidence of Effectiveness for Treatment of Refractory CMV Infection/Disease?

Issue

In Trial 303, differential treatment effects were observed in subjects with resistant and refractory CMV, with a smaller treatment difference observed between maribavir and IAT treatment arms in subjects with refractory CMV (without genotypic resistance) compared to subjects with resistant CMV.

Background

In Trial 303, all subjects enrolled had refractory CMV infection/disease. A subset of subjects had resistance-associated substitutions identified at baseline (to ganciclovir/valganciclovir, foscarnet or cidofovir). The latter group was referred to as the resistant subgroup, while those without resistance-associated substitutions identified were referred to as the refractory subgroup. All subjects were phenotypically resistant, and whether the distinction between resistant and refractory subgroups is clinically meaningful is debatable. The Advisory Committee considered these subgroups to be part of a continuum rather than distinct populations in the context of treatment because practically speaking, viral genotyping results may not be readily available at the time of treatment decisions in the setting of treatment failure. Nevertheless, the review team considered the distinction important in the context of the proposed indication and elected to review this issue in more detail.

In Trial 202, similar to Trial 303, all subjects had refractory CMV, defined as failure to achieve >1 $\log_{10}$ copies/mL decrease in CMV DNA level in blood/plasma after an interval of 2 or more weeks of treatment with valganciclovir/ganciclovir and/or foscarnet. Viral genotyping was performed, but due to problems with the assay used by the central laboratory, it is not clear how many subjects actually had genotypic resistance. Local laboratory data suggested that most subjects in Trial 202 had CMV that was genotypically resistant to ganciclovir, valganciclovir, or foscarnet, so no conclusions can be drawn from Trial 202 regarding maribavir efficacy in patients with refractory CMV without genotypic resistance.

Assessment

In Trial 303, most subgroups had results for the primary endpoint consistent with the overall analysis, and in most cases, response to maribavir was statistically significantly greater than in the IAT arm. However, there appeared to be a large difference in response rates favoring maribavir in resistant subjects (63% in maribavir subjects versus 20% in the IAT arm, CMH p<0.001) compared to little if any treatment difference in refractory subjects (44% in maribavir subjects versus 32% in the IAT arm, CMH p=0.17). There was a statistically significant difference in treatment effects between resistant and refractory subgroups (stratified Breslow-Day p=0.028). However, the treatment effect in both the subgroups were going in the same direction and therefore, it can be considered as only a quantitative interaction rather than as a qualitative interaction. In addition, the lack of a statistically significant treatment effect in the refractory patients could be due to limited sample size. See Table 28.

Table 28. Proportion of Subjects with CMV DNA <LLOQ at Week 8 (Randomized Patients)

	Number of Subjects (%)			
Subgroup	Maribavir 400 mg BID (n=235)	IAT (n=117)	Difference (95% CI)	p-Value
Resistant subjects	76 of 121 (63%)	14 of 69 (20%)	44% (31%, 57%)	<0.001
Refractory subjects	42 of 96 (44%)	11 of 34 (32%)	13% (-5%, +31%)	0.17

Source: Statistics reviewer's analysis.
Abbreviations: BID, twice daily; CI, confidence interval; CMV, cytomegalovirus; IAT, investigator-assigned treatment; LLOQ, lower limit of quantification

Conclusion

Although the treatment effect in the subgroup of subjects with refractory CMV (without genotypic resistance) was not statistically significant, the proportion of subjects who met the primary endpoint was higher in the maribavir group than the IAT group, and thus was consistent with the analysis in the overall population. Trial 303 was not powered to show statistical significance in subgroup analyses. In addition, the number of patients in the refractory subgroup was limited in comparison to the larger resistant CMV subgroup and hence the difference in the refractory subgroup may have been due to chance alone.

In clinical practice, if a patient has a refractory CMV infection or disease, treatment guidelines recommend empirical therapy (IV ganciclovir, sometimes at a higher than standard dose; or if the patient has severe tissue invasive disease, such as CMV pneumonia, foscarnet is recommended) until viral genotyping results are available. Viral genotyping results may not be readily available to initially identify optimal therapy. Maribavir may provide a treatment benefit in this population by providing improved tolerability in comparison to currently available drugs, and as shown in Trial 303, numerically higher efficacy than IAT in the refractory (without genotypic resistance group), trending in the same direction as in the overall population.

Generally, the review team agrees with the Advisory Committee that the distinction between resistant and refractory CMV is not clinically meaningful, as the virus is phenotypically resistant in both of these groups. As maribavir may provide clinical benefit in patients with either resistant or refractory CMV, approval in both subpopulations is indicated.

6.3.1.3. Does the Phase 2 Trial, SHP1263-202, Provide Supportive Evidence for the Efficacy of Maribavir for Treatment of Resistant/Refractory CMV Infection/Disease?

Issue

Trial 1263-202 was 'A Phase 2, Randomized trial to Assess the Safety and Anti-cytomegalovirus (CMV) Activity of Different Doses of Maribavir for Treatment of CMV Infections that are Resistant or Refractory to Treatment with Ganciclovir/Valganciclovir or Foscarnet in Transplant Recipients.' Trial 1263-202 had no active control arm, no dose response was demonstrated for the 400 mg BID, 800 mg BID and 1,200 mg BID doses, and baseline resistance was poorly defined in this study.

Background

This trial was a Phase 2, multicenter, randomized, dose-ranging, parallel-group study of maribavir for the treatment of CMV infections that were resistant or refractory to treatment with ganciclovir/valganciclovir or foscarnet in HSCT or SOT recipients. Eligible subjects were stratified by transplant type (HSCT or SOT) and randomized in a 1:1:1 allocation ratio to receive maribavir at 1 of 3 dose strengths (400 mg BID, 800 mg BID, or 1,200 mg BID) for up to 24 weeks. All subjects received maribavir. Resistance was defined as documentation of 1 or more valganciclovir/ganciclovir and/or foscarnet resistance-associated substitutions and failure to achieve >1 $\log_{10}$ copies/mL decrease in CMV DNA level in blood/plasma after an interval of 2 or more weeks of treatment with valganciclovir/ganciclovir and/or foscarnet. Refractory was defined as subjects without any valganciclovir/ganciclovir and/or foscarnet resistance-associated substitution(s) at baseline and failure to achieve >1 $\log_{10}$ decrease in CMV DNA level in blood/plasma after an interval of 2 or more weeks of treatment with valganciclovir/ganciclovir and/or foscarnet. The primary endpoint was the proportion of subjects with confirmed unquantifiable (<LLOQ) plasma CMV DNA within 6 weeks.

Assessment

This study had several deficiencies, including a small sample size of only 40 subjects per arm, and the lack of a control arm. Given the absence of a control arm, we can sometimes rely on a demonstration of a dose response to indicate activity of a drug, but in this trial there was no dose response.

The preliminary data from study SHP620-202 were encouraging in that maribavir appeared to have antiviral activity based on reductions in viral load and development of resistance. Seventy percent (28 of 40), 62.5% (25 of 40), and 67.5% (27 of 40) of subjects achieved CMV DNA <LLOQ within 6 weeks of treatment in the maribavir 400 mg BID, 800 mg BID, and 1,200 mg BID arms, respectively (Table 29). These rates were consistent regardless of the transplant type or dose received. However, the efficacy was substantially lower in subjects with high baseline viral load (≥10,000 copies/mL) compared to low baseline viral load (<10,000 copies/mL).

Table 29. Primary Efficacy Endpoint, Trial 202

Parameter	Maribavir 400 mg BID	Maribavir 800 mg BID	Maribavir 1,200 mg BID
Total	70.0% (28 of 40)	62.5% (25 of 40)	67.5% (27 of 40)
Subjects with missing data	0	0	5.0% (2 of 40)
Transplant type			
Solid organ transplant	70.8% (17 of 24)	58.3% (14 of 24)	69.6% (16 of 23)
Stem cell transplant	68.8% (11 of 16)	68.8% (11 of 16)	73.3% (11 of 15)
HCMV DNA viral load category			
Low	82.6% (19 of 23)	85.7% (18 of 21)	85.7% (18 of 21)
High	50.0% (8 of 16)	36.8% (7 of 19)	50% (8 of 16)

Source: FDA analysis.
Abbreviations: BID, twice daily; DNA, deoxyribonucleic acid; HCMV, human cytomegalovirus

Similar to the Phase 3 study, treatment-emergent maribavir resistance-associated substitutions at pUL97 amino acids F342, T409, and H411 were frequently observed. These resistance-associated substitutions were observed in 19 on-treatment virologic failures across all treatment arms and in 2 of those who experienced a relapse. Collectively, these data demonstrate the antiviral activity of maribavir.

However, there were issues with the Applicant's resistance analyses needed to support the resistance indication the Applicant is seeking (see resistance analysis section below). Briefly, ganciclovir/valganciclovir resistance-associated substitutions were absent in baseline isolates from a majority of the 120 subjects enrolled in Study SHP620-202 based on analyses conducted at the central laboratory. Resistance analyses results from the central laboratory found that baseline isolates from only three subjects had pUL97 ganciclovir/valganciclovir resistance-associated substitutions and isolates from 19 subjects had pUL54 substitutions associated with resistance to ganciclovir/valganciclovir, foscarnet, or cidofovir. In comparison, 62 subjects had pUL97 ganciclovir/valganciclovir resistance-associated substitutions and 16 subjects with pUL54 substitutions associated with resistance to ganciclovir/valganciclovir, foscarnet, or cidofovir based on the local laboratory results. Part of the discrepancy was due to genotyping at the central laboratory, which only covered pUL97 codons 270 to 482 and did not cover the ganciclovir resistance loci at codons 520 or 590 to 607. The Applicant was advised to include all pUL97 and pUL54 amino acid positions that were listed in the valganciclovir label, including pUL97 positions A591, E596, K599, and C603, for their genotypic analyses. The Applicant would likely have captured all of the resistance-associated substitutions that were missed by the central laboratory had they followed this recommendation.

The response rate based on the presence of baseline resistance-associated substitutions is summarized in Table 30.

Table 30. Confirmed CMV DNAemia <LLOQ at Week 6 (ITT) by Baseline Valganciclovir/Ganciclovir/Foscarnet/Cidofovir RAS, Trial 202

Conducting Laboratory	Maribavir 400 mg BID	Maribavir 800 mg BID	Maribavir 1,200 mg BID	Total
Central laboratory				
Yes	100% (2 of 2)	100% (3 of 3)	20% (1 of 5)	60% (6 of 10)
Local laboratory				
Yes	61.9% (13 of 21)	59.1% (13 of 22)	66.7% (14 of 21)	62.5% (40 of 64)
No	78.9% (15 of 19)	66.7% (12 of 18)	68.4% (13 of 19)	71.4% (40 of 56)

Source: FDA analysis.
Abbreviations: BID, twice daily; DNA, deoxyribonucleic acid; HCMV, human cytomegalovirus; ITT, intent-to-treat; LLOQ, lower limit of quantification; RAS, resistance-associated substitutions

Conclusion

This trial had no active control arm and failed to demonstrate a dose response. Furthermore, baseline resistance was poorly characterized in this study. Of note, the resistant population is a subset of the refractory population who were phenotypically resistant to their current therapy. However, similar to the Phase 3 study, several pUL97 maribavir specific resistant-associated substitutions developed at positions T409 and H411. These data further support the antiviral activity of maribavir. Therefore, based on the antiviral activity and resistance data demonstrated, this trial provides supportive evidence for antiviral activity in resistant/refractory CMV infection.

(b) (4)

2 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Nonclinical safety studies with maribavir included good laboratory practice repeat-dose toxicology studies in mice, rats, and monkeys; reproductive and developmental toxicology studies in rats and rabbits; in vitro and in vivo safety pharmacology and genotoxicity studies; and 2-year carcinogenicity studies in mice and rats. Overall, the nonclinical safety assessment for maribavir was considered acceptable to support marketplace approval from a pharmacology/toxicology perspective. Exposure multiples mentioned in the summary text are based on total maribavir concentration. All pertinent studies and findings are summarized in the following section. Full reviews for all studies are located in Section III.13.2.

7.1.1. Pharmacology

A profiling panel of in vitro and in vivo tests was performed to identify possible off-target activity of maribavir, including its broad pharmacological effects on the central nervous system, cardiovascular system, and GI systems, as well as on metabolic, inflammation and allergy, and microbiological activity. In summary, no significant activity was observed at the dose levels and concentrations tested. See Section III.18 for studies on mechanism of action and antiviral activity.

Maribavir did not inhibit human ether-à-go-go-related gene in vitro at target concentrations up to 1,500 µg/mL, providing a wide safety margin of more than 4000-fold the clinical C_{max} (unbound 0.344 µg/mL) value, with 400 mg BID dose. In anesthetized dogs, a transient increase in heart rate was observed following the 30 mg/kg IV dose, and both respiratory rate and volume were transiently increased following the 10 mg/kg and 30 mg/kg doses. There were no changes in electrocardiogram parameters in repat dose toxicology studies in monkeys. A thorough QT interval study demonstrated no clinically significant repolarization effect of maribavir administration at single oral doses of 100 mg or 1,200 mg in healthy human subjects.

7.1.2. Pharmacokinetics

Oral bioavailability of maribavir was moderate to high across species at 69% in mice, 92% to 98% in rats, and 42% to 112% in monkeys. In vitro, maribavir was moderately bound to plasma proteins in mice, rats, rabbits, and monkeys at 84.7% to 93.8%, 82.7% to 88.3%, 89.7%, and 83.9% to 91.7%, respectively, and highly bound in humans at 98%. VP 44469 (major human metabolite) was less protein bound than maribavir except in rabbit plasma, where the binding was comparable (76.1%, 71.4%, 90.9%, and 78.3%, in mouse, rat, rabbit, and monkey, respectively). Half-life after oral administration was 1.6 to 8.5 hours in mice, 22 to 44 hours in rats, and 10 to 13 hours in monkeys.

In a rat distribution study, the highest concentrations of maribavir were observed in the kidney cortex, kidney, and liver. Maribavir was shown not to cross the blood brain barrier to any measurable extent in rats. In a 28-day repeat dose monkey toxicology study, concentrations of maribavir in vitreous humor were below 1% of corresponding plasma levels. Brain concentrations ranged from about 3.5% to 20% of plasma levels.

In vivo studies demonstrated that maribavir was primarily metabolized in the liver after systemic absorption in mice, rats, and monkeys, where it is biotransformed predominantly by CYP3A-catalyzed oxidative metabolism via primary pathways of oxidation, N-dealkylation, N-glycosidic bond hydrolysis, and glucuronidation. VP 44469 (N-dealkylation of the isopropyl group) has been shown to be a metabolite in mice, rats, monkeys, and major metabolite in humans. The AUC ratio of VP 44469 to maribavir in human plasma has been observed between 14% and 35%. See Section III.14 for more details. The AUC ratio of VP 44469 to maribavir in mouse, rat and monkey in pivotal toxicology studies was approximately 37%, 12%, and 14%, respectively. As such, the safety of VP 44469 has been assessed based on systemic exposure in nonclinical species. Biliary excretion and metabolism were the major routes of elimination in mice, rats, and monkeys. In humans, following oral administration, maribavir was primarily eliminated by hepatic metabolism followed by urinary and fecal excretion of the metabolites.

7.1.3. General Toxicology

The acute toxicity and tolerability of maribavir was evaluated in single dose intravenous and oral toxicity studies in both CD-1 mice and Sprague-Dawley rats. Mortality was observed in mice at doses ≥500 mg/kg, and ≥1,000 mg/kg in rats. Clinical signs of toxicity in mice included: prostration, convulsions, vocalization, together with gasping and ataxia in a subset of mice at 1,000 mg/kg dose. Clinical signs of toxicity in rats included: salivation, decreased activity, labored breathing, tremors, prostration, and soft feces.

Pivotal repeat-dose toxicology evaluations for maribavir included good laboratory practice studies of up to 52 weeks duration in monkeys, 26 weeks duration in rats and 13 weeks duration in mice; studies in mice were conducted in support of the 2-year carcinogenicity study in CD-1 mice. In the repeat-dose toxicology studies, mortality was observed in mice at doses ≥300 mg/kg/day, and in rats at 400 mg/kg/day in the chronic 26-week study. In the 52-week monkey study, 2 males at 400/300 mg/kg/day (two dose levels indicate dose adjustment during the study) and 1 male at 200 mg/kg/day were euthanized in extremis. The major findings in the 52-week study in monkeys and 26-week study in rats were regenerative anemia and gastrointestinal effects (GI effects; histologic change of mucosal cell hyperplasia in the intestinal tract associated with clinical observations of soft to liquid stool and dehydration), which were reversible or showed progression to recovery after cessation of dosing. Although changes in the intestinal tract were apparent in all pivotal toxicology studies in rats (30-day and 26-week), they were not observed in the 30-day toxicology study in monkeys. The key toxicities (GI and hematological effects) in monkeys and rats were reversible upon discontinuation of treatment and are clinically monitorable by routine observation or by non-invasive tests such as hematology. The exposures at the no observed adverse effect levels/lowest observed adverse effect levels in the 52-week monkey study, 26-week rat study, and 13-week mouse study were less than the human exposures at the recommended human dose (RHD).

In clinical trials, the most notable adverse events associated with maribavir were mild to moderate dysgeusia, nausea, and diarrhea, thus reflecting the main toxicities observed in nonclinical species.

7.1.4. Genotoxicity and Carcinogenicity

Maribavir was negative for mutagenesis in the in vitro bacterial reverse mutation assay and clastogenicity in the in vivo micronucleus assay in rats. However, in mouse lymphoma assays (in

vitro), a weak clastogenic potential in the absence of exogenous metabolic activation (rat liver S9) was identified. Results with S9 were equivocal. Although maribavir demonstrated mutagenic potential in the absence of metabolic activation in the mouse lymphoma assay, given the negative results of the in vivo rat micronucleus assay and the negative bacterial mutation assay, the weight of evidence indicates that maribavir does not exhibit genotoxic potential.

Two-year carcinogenicity studies were conducted in mice and rats administered oral doses up to 150 and 100 mg/kg/day, respectively. Maribavir was not carcinogenic in rats at any dose tested, corresponding to maribavir exposures less than human exposure at the RHD. At 150 mg/kg/day in male mice only, an increased incidence of hemangiosarcoma and combined hemangioma/ hemangiosarcoma was observed across multiple tissues at exposures less than the human exposure at the RHD. There were no carcinogenic findings in male mice at ≤75 mg/kg/day and female mice at any dose.

7.1.5. Reproductive and Developmental Toxicology

In a combined fertility and embryofetal development study, maribavir was administered to male and female rats at oral doses of 100, 200, or 400 mg/kg/day. Females were dosed for 15 consecutive days prior to pairing, throughout pairing, and up to gestation day (GD) 17, while males were dosed 29 days prior to mating and throughout mating. A decrease in the number of viable fetuses, and increase in early resorptions and post-implantation losses were observed at ≥100 mg/kg/day (at exposures approximately half the human exposure at the RHD). Intermittent reduced body weight gain was observed in pregnant animals at ≥200 mg/kg/day. In addition, although decreased sperm straight line velocity was observed in males (at all doses), there were no effects on fertility in males or females at up to 400 mg/kg/day. Maribavir had no effect on embryo-fetal growth or development in rats, at dose levels up to 400 mg/kg/day, corresponding to exposures similar to those observed at the RHD.

There were no drug-related effects on embryo-fetal growth or development in rabbits at exposures less than human exposures at the RHD.

In the pre-and postnatal developmental toxicity study maribavir was administered to pregnant rats at oral doses of 50, 150, or 400 mg/kg/day from GD 7 to postnatal day (PND) 21. A delay in developmental milestones was observed, including pinna detachment at doses ≥150 mg/kg/day and eye opening and preputial separation associated with reduced bodyweight gain of the offspring at 400 mg/kg/day. In addition, decreased fetal survival and litter loss was observed due to maternal toxicity and poor maternal care, respectively, at doses ≥150 mg/kg/day. No effects were observed at 50 mg/kg/day (which is estimated to be less than the human exposure at the RHD). No effects on number of offspring, proportion of males, number of live pups, or survival to PND 4 were observed at any dose in the offspring born to the second generation.

Maribavir was evaluated in three 4-week juvenile toxicity studies in rats. In all the juvenile toxicity studies, rats were dosed from PND 7 to 34, followed by 2 weeks or 1 month of postdose recovery; juvenile rats were dosed up to 300/225 mg/kg/day (males/females), in pivotal studies. There were no significant maribavir-related findings in the pivotal juvenile toxicology studies, and the highest doses tested were the study no observed adverse effect levels. Exposures in pivotal juvenile toxicology studies at the no observed adverse effect level reached up to 389 μg·h/mL (AUC_{0-24}) and 23.6 μg/mL (C_{max}), corresponding to exposures similar to or less than those observed in humans (adult) at the RHD.

7.1.6. Additional Toxicology Studies

Maribavir did not produce a phototoxic response in the neutral red uptake phototoxicity assay at concentrations up to 100 μg/mL. Maribavir (57 mg) was irritant to the eyes of rabbits, but there was no evidence of irritant effects when applied dermally to rats (2000 mg/kg), rabbits (500 mg), or guinea pigs (1% w/v). Maribavir was not immunotoxic in rats at up to 100 mg/kg/day.

7.1.7. Exposure Multiples

Exposure multiples, based on a proposed human dose of 400 mg BID and based on total and free unbound concentration, are presented in Table 33 and Table 34 for maribavir and maribavir metabolite VP 44469, respectively.

Table 33. Maribavir Exposure Multiples Based on the NOAEL/LOAEL in Toxicology Studies

Study Number	Study Description[a]	NOAEL/ LOAEL Dose (mg/kg/day)	Total Concentration		Free Unbound Concentration[b]		Total Concentration		Free Unbound Concentration	
			C_{max} (µg/mL)	AUC_{0-24} (µg·h/mL)	C_{max} (µg/mL)	AUC_{0-24} (µg·h/mL)	Margin[c] C_{max}	Margin[c] AUC_{0-24}	Margin C_{max}	Margin AUC_{0-24}
Mouse										
M9582M-SHP620 (BB 1596)	13-week Mouse (M)	150	19.7	99.2	3.01	15.18	1.15	0.39	8.76	2.96
	13-week Mouse (F)		19.9	105	3.04	16.07	1.16	0.41	8.85	3.14
M9526M-SHP620 (BB 1710)	2-year Carcinogenicity Mouse (M)	75[d]	8.75	90	1.34	13.77	0.51	0.35	3.89	2.69
	2-year Carcinogenicity Mouse (F)		10.1	63.5	1.55	9.72	0.59	0.25	4.49	1.90
Rat										
R9554M-SHP620 (VP 1205)	28-day Rat (M)	200	7.49	97.82	0.89	11.64	0.44	0.38	2.59	2.27
	28-day Rat (F)		15.24	204.3	1.81	24.31	0.89	0.80	5.27	4.75
R9568M-SHP620 (VP 1225)	30-day Rat (M)	100[e]	3.62	54.3[f]	0.43	6.46	0.21	0.21	1.25	1.26
	30-day Rat (F)		7.5	106.3[f]	0.89	12.65	0.44	0.42	2.59	2.47
R9549M-SHP620 (VP 1196)	26-week Rat (M)	25	1.28	12.98	0.15	1.54	0.07	0.05	0.44	0.30
	26-week Rat (F)		4.39	26.75	0.52	3.18	0.26	0.10	1.52	0.62
R9558M-SHP620 (VP 1210)	Fertility & Embryofetal Development Rat (F)	100	9.57	126.74	1.14	15.08	0.56	0.50	3.31	2.95
R10949M-SHP620	Juvenile Rat DRF (Day 7)	100	22.15	386	2.64	45.93	1.29	1.51	7.66	8.97
	Juvenile Rat DRF (Day 34)		6.3	46.35	0.75	5.52	0.37	0.18	2.18	1.08
R11007M-SHP620	Juvenile Rat Definitive 1 (Day 7)	100	23.6	389	2.81	46.29	1.37	1.52	8.16	9.04
	Juvenile Rat Definitive 1 (Day 34)		5.23	68.1	0.62	8.10	0.30	0.27	1.81	1.58
R11521M-SHP620	Juvenile Rat Definitive 2 (Day 7)[g]	25	10.95	182	1.30	21.66	0.64	0.71	3.79	4.23
	Juvenile Rat Definitive 2 (Day 34)[g]	300/225	11.7	96.95	1.39	11.54	0.68	0.38	4.05	2.25

Continued on next page.

Study Number	Study Description[a]	NOAEL/ LOAEL Dose (mg/kg/day)	Total Concentration		Free Unbound Concentration[b]		Total Concentration		Free Unbound Concentration	
			C_{max} (µg/mL)	AUC_{0-24} (µg•h/mL)	C_{max} (µg/mL)	AUC_{0-24} (µg•h/mL)	Margin[c] C_{max}	Margin[c] AUC_{0-24}	Margin C_{max}	Margin AUC_{0-24}
R9581M-SHP620 (VP 1570)	2-year Carcinogenicity Rat (M)	100[d]	4.88	50.1	0.58	5.96	0.28	0.20	1.69	1.16
	2-year Carcinogenicity Rat (F)		10.2	92.6	1.21	11.02	0.59	0.36	3.53	2.15
Rabbit										
L9541M-SHP620 (VP 1187)	Embryofetal Development - Rabbit (F)	100	23.05	114.16	2.38	11.78	1.34	0.45	6.92	2.30
Monkey										
P9537M-SHP620 (VP 1178)	28-day DRF Monkey	180	12.2	100.6[h]	1.96	16.20	0.71	0.39	5.71	3.16
P9559M-SHP620 (VP 1211)	30-day Monkey	180	6.65	58.4[i]	1.07	9.40	0.39	0.23	3.11	1.84
P9539M-SHP620 (VP 1182)	26-week Monkey	50/100[e,j]	2.97	41.07	0.48	6.61	0.17	0.16	1.39	1.29
P9538M-SHP620 (VP 1181)	52-week Monkey	100[e]	4.52	64.99	0.73	10.46	0.26	0.25	2.12	2.04

AUC_{0-24}=area under the concentration-versus time curve from 0 hours to 24 hours; AUC_{0-8}=area under the concentration-versus time curve from 0 hours to 8 hours; $AUC_{0-\tau(ss)}$=area under the curve of a dosing interval at steady state; BID=twice daily; C_{max}=maximum concentration; $C_{max(ss)}$=maximum concentration at steady state; CMV=cytomegalovirus; DRF=dose range-finding; F=female; h=hour; LOAEL=lowest-observed-adverse-effect level; M=male; NOAEL=no-observed-adverse-effect level; PK=pharmacokinetic

[a] Unless otherwise specified, sex-combined exposures are used for exposure multiple calculation.

[b] Plasma protein binding of maribavir is 84.7%, 88.1%, 89.68%, 83.9%, and 98% (free fractions of 15.3%, 11.9%, 10.32%, 16.1% and 2%) in mouse, rat, rabbit, monkey, and human plasma, respectively (V9054M-SHP620 [VP 1233]; rabbit from V9071M-SHP620 [VP 1585]).

[c] Margins are calculated based on steady-state exposure of maribavir in CMV patients following 400 mg BID doses based on the final population PK report where $C_{max(ss)}$=17.2 µg/mL and $AUC_{0-\tau(ss)}$=128 µg•h/mL. Estimated AUC_{0-24} was calculated as 2×$AUC_{0-\tau(ss)}$=256 µg•h/mL.

[d] Doses and exposures where no carcinogenicity findings were observed.

[e] NOAELs were not determined in these studies; the indicated dose and exposure represent the LOAELs.

[f] Plasma samples were collected 0 (prior to dose), 2, 5, and 8 hours postdose. The plasma AUC_{0-24} was calculated from the average concentration at each time, using the linear trapezoid method. The predose sample was used for the time 0 sample, as well as for the 24-hour sample postdose.

[g] Maribavir doses were titrated in the study to keep constant exposure throughout the study. On Day 7, the high dose was 25 mg/kg/day for both males and females. On Day 34, the doses were 300 mg/kg/day for males and 225 mg/kg/day for females.

[h] Study P9537M-SHP620 (VP 1178): AUC_{0-8}=50.3 µg•h/mL, dosed as 90 mg/kg BID, therefore estimated AUC_{0-24} is calculated as 2×AUC_{0-8}=100.6 µg•h/mL.

[i] Study P9559M-SHP620 (VP 1211): AUC_{0-8}=29.2 µg•h/mL, dosed as 90 mg/kg BID, therefore estimated AUC_{0-24} is calculated as 2×AUC_{0-8}=58.4 µg•h/mL.

[j] Study P9539M-SHP620 (VP 1182): for the first 3 weeks, maribavir dose was 50 mg/kg/day and for the remainder of the study the dose was 100 mg/kg/day.

Note: Exposure multiples were prepared relative to total ($C_{max, total}$; AUC_{total}) and free unbound ($C_{max\ free}$; AUC_{free}) exposures of maribavir.

Source: Table 22 of the Toxicology Written Summary.

Table 34. VP 44469 (Maribavir Metabolite) Exposure Multiples Based on the NOAEL/LOAEL in Toxicology Studies

Study Number	Study Description[a]	NOAEL/ LOAEL Dose (mg/kg/day)	Total Concentration		Free Unbound Concentration[b]		Total Concentration		Free Unbound Concentration	
			C_{max} (µg/mL)	AUC_{0-24} (µg•h/mL)	C_{max} (µg/mL)	AUC_{0-24} (µg•h/mL)	Margin[c] C_{max}	Margin[c] AUC_{0-24}	Margin C_{max}	Margin AUC_{0-24}
Mouse										
M9582M-SHP620 (BB 1596)	13-week Mouse (M)	150	11.6	143	2.77	34.18	7.48	5.46	17.89	13.04
	13-week Mouse (F)		6.94	39.4	1.66	9.42	4.48	1.50	10.70	3.59
M9526M-SHP620 (BB 1710)	2-year Carcinogenicity Mouse (M)	75[d]	5.12	67.9	1.22	16.23	3.30	2.59	7.89	6.19
	2-year Carcinogenicity Mouse (F)		4.18	24.3	1.00	5.81	2.70	0.93	6.45	2.22
Rat										
R9549M-SHP620 (VP 1196)	26-week Rat (M)	25	0.048	NA	0.01	NA	0.03	NA	0.09	NA
	26-week Rat (F)		0.24	2.98	0.07	0.85	0.15	0.11	0.44	0.33
R9581M-SHP620 (VP 1570)	2-year Carcinogenicity Rat (M)	100[d]	0.343	2.38[e]	0.10	0.68	0.22	0.09	0.63	0.26
	2-year Carcinogenicity Rat (F)		0.917	10[e]	0.26	2.86	0.59	0.38	1.69	1.09
Monkey										
P9537M-SHP620 (VP 1178)	28-day DRF Monkey	180	1.3	11.8[f]	0.28	2.56	0.84	0.45	1.82	0.98
P9539M-SHP620 (VP 1182)	26-week Monkey	50/100[g,h]	0.54	6.8	0.12	1.48	0.35	0.26	0.76	0.56
P9538M-SHP620 (VP 1181)	52-week Monkey	100[g]	0.658	9.41	0.14	2.04	0.42	0.36	0.92	0.78

AUC_{0-24}=area under the concentration-versus time curve from 0 hours to 24 hours; AUC_{0-8}=area under the concentration-versus time curve from 0 hours to 8 hours; $AUC_{0-\tau(ss)}$=area under the curve of a dosing interval at steady state; BID=twice daily; C_{max}=maximum concentration; $C_{max(ss)}$=maximum concentration at steady state; DRF=dose range finding; F=female; h=hour; LOAEL=lowest-observed-adverse-effect level; M=male; NA=not available; NOAEL=no-observed-adverse-effect level

[a] Unless otherwise specified, sex-combined exposures are used for exposure multiple calculation.

[b] Plasma protein binding of VP 44469 is 76.1%, 71.4%, 78.3%, and 90% (free fractions of 23.9%, 28.6%, 21.7%, and 10%) in mouse, rat, monkey, and human plasma, respectively (V9071M-SHP620 [VP 1585]; Clinical Study CMAB1002).

[c] Margins are calculated based on steady-state exposure of maribavir in healthy subjects following 400 mg BID doses where Day 3 $C_{max(ss)}$=1.55 µg/mL and $AUC_{0-\tau(ss)}$=13.1 µg•h/mL. Estimated AUC_{0-24} was calculated as 2×$AUC_{0-\tau(ss)}$=26.2 µg•h/mL (Clinical Study 1263-110).

[d] Doses and exposures where no carcinogenicity findings were observed.

[e] Study R9581M-SHP620 (VP 1570): AUC_{0-last} values are reported because AUC_{0-24} values were not determined due to very low exposures.

[f] Study P9537M-SHP620 (VP 1178): AUC_{0-8}=5.9 µg•h/mL, dosed as 90 mg/kg BID, therefore estimated AUC_{0-24} is calculated as 2×AUC_{0-8}=11.8 µg•h/mL

[g] NOAELs were not determined in these studies; the indicated dose and exposure represent the LOAELs.

[h] Study P9539M-SHP620 (VP 1182): for the first 3 weeks, maribavir dose was 50 mg/kg/day and for the remainder of the study the dose was 100 mg/kg/day.

Note: Exposure multiples were prepared relative to total ($C_{max,\ total}$; AUC_{total}) and free unbound ($C_{max,free}$; AUC_{free}) exposures of VP 44469.

Source: Table 23 of the Toxicology Written Summary.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Maribavir is an orally bioavailable benzimidazole riboside antiviral with a novel mechanism of action against CMV. It targets CMV pUL97, which not only results in inhibition of viral DNA replication, but also encapsidation and nuclear egress. Currently available anti-CMV agents are DNA polymerase inhibitors, targeting the virus at UL54, a location on the viral genome controlling DNA replication. Thus, there are no drug class specific risk factors. Benzimidazole rings are in a structural class associated with mutagenicity. However, maribavir is structurally related to several over-the-counter drugs, such as proton pump inhibitors. As such, there is not much concern with toxicity based on maribavir structure and associated impurities.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

Not applicable. This drug has not yet been approved in any country.

7.4. FDA Approach to the Safety Review

Data from the Phase 3 Trial 303 (pivotal data) and the two Phase 2 Trials 202 and 203 (supportive data) formed the basis of the clinical safety evaluation.

Pivotal Data

The safety evaluation of this NDA is based primarily on the Phase 3 Trial 303, a multicenter, open-label, active-controlled trial designed to assess the safety and efficacy of maribavir compared to IAT for the treatment of post-transplant CMV infections in HSCT and SOT transplant recipients which were resistant or refractory to treatment to ganciclovir, valganciclovir, foscarnet or cidofovir. In Trial 303, a total of 352 subjects fulfilling the entry criteria were randomized in a 2:1 ratio to receive either maribavir 400 mg twice daily or IAT for 8 weeks. Upon completion of the treatment period, enrolled subjects entered a 12-week follow-up period (see Section 6.2.1 for further details of the design of this trial).

Supportive Data

To further support the NDA package the Applicant submitted data from the two Phase 2 trials:

- *Trial 202*: This was randomized, dose-ranging trial in subjects ≥12 years of age who had undergone HSCT or SOT and had CMV infection which was resistant or refractory to treatment with ganciclovir/valganciclovir or foscarnet. A total of 120 eligible subjects were stratified by transplant type (HSCT or SOT) and were randomized in a 1:1:1 ratio to receive oral maribavir 400 mg BID, 800 mg BID or 1,200 mg BID. All subjects received maribavir, but subjects and investigators were blinded to maribavir dose. At the Week 3 visit, and based on the Week 2 CMV test results, subjects who had demonstrated any decrease in CMV DNA levels were allowed to continue study drug at the discretion of the Investigator. Subjects still receiving study drug through Week 6 continued treatment with study drug if the Week 5 CMV test results demonstrated a ≥2 $\log_{10}$ decrease from baseline or undetectable CMV DNA levels. For subjects who continued dosing after the

Week 6 visit, dosing was continued at the discretion of the Investigator through a maximum of 24 weeks in an attempt to decrease CMV DNA to undetectable and/or to maintain undetectable CMV DNA levels.

- *Trial 203:* This was a randomized, dose-ranging, parallel-group of maribavir versus valganciclovir for the treatment of CMV infections in subjects ≥18 years of age who had undergone HSCT or SOT and had CMV infection without CMV organ disease or a CMV infection known to be resistant to available CMV drugs. A total of 159 eligible subjects stratified by transplant type (HSCT or SOT) were randomized in a 1:1:1:1 ratio to receive oral maribavir at one of three doses (400 mg BID: 40 subjects, 800 mg BID: 40 subjects or 1,200 mg BID: 39 subjects) or valganciclovir (40 subjects). Regarding subjects who received maribavir, investigators, and study staff were blinded to maribavir dose. At the Week 3 visit, and based on the Week 2 CMV test results, subjects who have demonstrated any decrease in CMV DNA levels were allowed to continue treatment. At Week 6, subjects needed to have Week 5 results demonstrating ≥2 $\log_{10}$ decrease from baseline to continue study drugs. For subjects who continued dosing after the Week 6 visit, dosing was continued at the discretion of the Investigator through a maximum of 12 weeks in an attempt to decrease CMV DNA to undetectable, and/or to maintain undetectable CMV DNA in an effort to prevent recurrence.

Safety data from the Phase 2 and 3 trials were not pooled because of differences in study design, trial population (resistant or refractory versus asymptomatic CMV viremia), maribavir doses, and duration of treatment.

7.5. Adequacy of Clinical Safety Database

Overall, CMV infection in transplant patients is considered a rare disease and resistant or refractory CMV infection comprises a small subset of this population. Please also note that maribavir received an orphan drug designation and breakthrough therapy designation.

Because CMV disease is serious and life-threatening in transplant patients, a safety database of 300 to 500 patients who received the proposed dose and duration of the drug is considered sufficient for prophylaxis trials. However, for marketing applications evaluating trials with resistant or refractory CMV infection a safety database of approximately 300 patients is considered adequate. In the Phase 3 trial, 224 subjects received maribavir 400 mg BID for at least 45 days; 202 subjects in the maribavir arm and 22 subjects in the IAT arm who switched to the rescue arm. These patients, together with supportive data from 124 subjects from the Phase 2 trials who received maribavir 400 mg BID or higher doses for at least 56 days, meet the requirements outlined in the FDA Guidance for Industry: *Cytomegalovirus in Transplantation: Developing Drugs to Treat or Prevent Disease*.[1] Duration of maribavir exposure in Trials 303, 202, and 203 is shown in Table 35, Table 36, and Table 37.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www fda.gov/regulatory-information/search-fda-guidance-documents.

Table 35. Duration of Exposure, Safety Population, Trial 303

Parameter	Maribavir 400 mg BID N=234 n (%)	IAT N=116 n (%)
Duration of treatment (days)		
Mean (SD)	52 (13)	36 (18)
Median (minimum, maximum)	57 (2, 64)	34 (4, 64)
Subjects treated, by duration		
Any duration (at least one dosage)		
<15 days	10 (4%)	18 (16%)
≥15 days to <30 days	12 (5%)	36 (31%)
≥30 days to <45 days	10 (4%)	15 (13%)
≥45 days to <60 days	189 (81%)	44 (38%)
≥60 days	13 (6%)	3 (3%)

Source: adex.xpt; software, R.
Abbreviations: BID, twice daily; IAT, investigator-assigned treatment; N, number of subjects in group; n, number of subjects with given treatment duration; SD, standard deviation

Table 36. Duration of Exposure, Safety Population, Trial 202

Variable	Maribavir 400 mg BID N=40	Maribavir 800 mg BID N=40	Maribavir 1,200 mg BID N=40	Maribavir Total N=120
Duration of exposure, days				
Mean (SD)	86 (56)	87 (53)	90 (62)	88 (57)
Median (minimum, maximum)	72 (9, 177)	80 (7, 174)	72(5, 176)	75 (42, 156)
Subjects treated, by duration, n (%)				
<14 days	1 (3)	3 (8)	5 (13)	9 (8)
≥14 to <28 days	5 (13)	2 (5.0)	4 (10.0)	11 (9)
≥28 to <56 days	9 (23)	10 (25)	4 (10)	23 (19)
≥56 to <84 days	9 (23)	5 (13)	10 (25)	24 (20)
≥84 to <112 days	4 (10)	5 (13)	2 (5)	11 (9)
≥112 days	12 (30)	15 (38)	15 (38)	42 (35)

Source: adex.xpt; software, R.
Abbreviations: BID, twice daily; IAT, Investigator assigned treatment; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; SD, standard deviation

Table 37. Duration of Exposure, Safety Population, Trial 203

Variable	Maribavir 400 mg BID N=40 n (%)	Maribavir 800 mg BID N=40 n (%)	Maribavir 1,200 mg BID N=39 n (%)	Maribavir Total N=119 n (%)	Valganciclovir 900 mg BID N=40 n (%)
Duration of exposure, days					
Mean (SD)	51 (29)	48 (23)	48 (32)	49 (28)	45 (31)
Median (min, max)	45 (1, 96)	43 (3, 88)	45 (2, 89)	45 (1, 96)	33 (1, 88)
Subjects treated, duration					
<7 days	2 (5)	1 (3)	5 (13)	8 (7)	3 (8)
≥7 to <14 days	2 (5)	1 (3)	1 (3)	4 (3)	3 (8)
≥14 to <28 days	6 (15)	6 (15)	7 (18)	19 (16)	9 (23)
≥28 to <56 days	13 (33)	19 (48)	9 (23)	41 (34)	10 (25)
≥56 to <84 days	7 (18)	8 (20)	7 (18)	22 (18)	4 (10)
≥84 days	10 (25.0)	5 (12.5)	10 (26)	25 (21)	11 (28)

Source: adex.xpt; software, R.
Abbreviations: BID, twice daily; IAT, investigator-assigned treatment; max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; SD, standard deviation

7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

7.6.1. Safety Findings and Concerns, Trial 303

7.6.1.1. Overall Treatment-Emergent Adverse Event Summary, Trial 303

Table 38 summarizes the treatment-emergent adverse events (TEAEs) from clinical Trial 303. Almost all subjects experienced at least one TEAE. This is not unexpected considering the underlying disease and associated treatment. A somewhat higher proportion of subjects in the maribavir arm experienced at least one TEAE than in the IAT arm. This may be due to the longer duration of exposure in the maribavir than the IAT arm, as duration of exposure to maribavir was almost 50% longer compared to duration of exposures to IAT drugs. In Trial 303, the proportion of subjects with serious adverse events (SAEs), SAEs with fatal outcome, AEs leading to modification of study group were similar between the maribavir group and the IAT group. However, a higher percentage of subjects in the IAT group discontinued treatment due to AEs compared to subjects in the maribavir group (32% versus 13%).

Table 38. Overview of Treatment-Emergent Adverse Events During the Treatment Period, Controlled Trial Safety Population, Trial 303

Event	Maribavir N=234 n (%)	IAT N=116 n (%)	Risk Difference (95% CI)
Any treatment-emergent AE[1]	228 (97%)	106 (91%)	6 (1, 12)
Severe AEs	75 (32%)	44 (38%)	-6 (-17, 5)
SAEs	90 (38%)	43 (37%)	1 (-9, 12)
SAEs with fatal outcome	16 (7%)	6 (5%)	2 (-3, 7)
AEs leading to discontinuation of study drug	31 (13%)	37 (32%)	-19 (-28, 9)
AEs leading to dosage modification of study drug	13 (6%)	8 (7%)	-1 (-7, 4)
AEs leading to interruption of study drug	13 (6%)	5 (4%)	1 (-3, 6)
AEs leading to reduction of study drug	0	4 (3%)	-3 (-7, 0)
AEs leading to dosage delay of study drug	0	0	0 (0, 0)

Source: adae.xpt; software, R.
[1] Includes treatment-emergent AE defined as an AE that had start date on or after the first dose of study-assigned treatment or that had a start date before the date of the first dose of study-assigned treatment but increased in severity after the first dose of study assigned treatment. 2 NCI CTCAE (4.03)
Duration is 8 weeks.
Abbreviations: AE, adverse event; SAE, serious adverse event; CI, confidence interval; IAT, investigator-assigned treatment; N, number of subjects in group; n, number of subjects with at least one event

7.6.1.2. Deaths, Trial 303

There was no difference in all-cause mortality between the two treatment groups. There were 27 (11%) deaths in the maribavir group and 13 (11%) deaths in the IAT group. Among the deaths there were four subjects (two in each group) who died after the 20-week study observation period. These 4 deaths were captured because they were associated with serious adverse events which were ongoing after the completion of the 12-week follow-up period (Study Week 20). The timing of the deaths is summarized in Table 39.

Table 39. All-Cause Mortality and Timing of Deaths in Trial 303

Deaths	Maribavir N=235 n (%)	IAT N=117 n (%)
Reported deaths at any time during the trial	27 (11)	13 (11)
During the first 8 weeks of the trial	14 (6)	5 (4)
Week 9 to Week 20 of the trial	11	6
After Week 20 of the trial	2	2

Source: adae.xpt; Software R; Narratives of deaths.
Abbreviation: IAT, investigator-assigned treatment; N, number of subjects in study arm; n, number of subjects within specified category

With respect to the onset of SAEs that resulted in death, a total of 38 subjects experienced fatal SAEs in the overall study period (on-treatment or during post-treatment period); 26 (11%) in the maribavir group and 12 (10%) in the IAT group. Most SAE preferred terms leading to death were reported for one subject each. The most common SAEs leading to death were due to respiratory failure or relapse/worsening of the underlying disease.

Twenty-two of the 38 subjects who experienced fatal SAEs, had treatment-emergent serious adverse events (TESAEs, during the on-treatment period); 16 (7%) subjects in the maribavir group and 6 (5%) in the IAT group. There was no consistent pattern of fatal TESAEs within each group or between the two groups. The only TESAEs with fatal outcome reported in more than one subject during the on-treatment period were: respiratory failure (three subjects, 2 in the maribavir group and 1 in the IAT group), acute myeloid leukemia (recurrent) (one subject in each treatment group), and leukemia (recurrent) (one subject in each treatment group). Fatal TESAEs due to any CMV infection during the on-treatment period were reported in two subjects in the maribavir group and one subject in the IAT group.

Of the 16 subjects who experienced fatal SAEs during the off-treatment period, 10 (4%) were in the maribavir group and 6 (4%) in the IAT group. These most common post-treatment SAEs with fatal outcome were consistent with progression of the underlying disease. Fatal SAEs due to any CMV infection during the post-treatment period were reported for 2 maribavir subjects and 2 IAT-treated subjects.

Only two fatal TESAEs (one in each group) were considered by the investigators as related to study-assigned treatment (see Section III.17.1.1 for a brief description of these two cases).

Overall, the analysis of fatal events does not reveal any specific risks associated with study-assigned treatments. The causes of deaths for the 27 subjects in the maribavir group and the 13 subjects in the IAT group are summarized in Table 126.

7.6.1.3. Serious Adverse Events, Trial 303

Non-fatal serious treatment-emergent adverse events were reported in 38% of subjects in the maribavir group and 37% of subjects in the IAT group. However, it should be noted that the duration of exposure to maribavir was approximately 50% longer than the exposure to the IAT drugs. In both treatment groups, most TESAEs were reported for one subject only. TESAEs most commonly occurred in the Infections and Infestations system organ class (SOC, maribavir 23%, IAT 15%). The higher proportion of infections in the maribavir group was probably due to the longer duration of treatment with maribavir compared to the IAT group. However, a higher percentage of subjects in the IAT group discontinued treatment drug due to SAEs compared to subjects in the maribavir group (15% [17 of 116] of the subjects randomized to IAT versus 8.5%

[20 of 234] subjects randomized to maribavir). Table 40 summarizes the most common TESAEs reported by 3 or more subjects in either treatment group.

Table 40. Treatment-Emergent Serious Adverse Events Reported by 3 or More Subjects in Either Group, Safety Population, Trial 303

Serious Adverse Event[1]	Maribavir N=234 n (%)	IAT N=116 n (%)
Acute kidney injury	8 (3)	4 (3)
Cytomegalovirus viremia	7 (3)	3 (3)
Cytomegalovirus infection	6 (3)	4 (3)
Diarrhea	4 (2)	0
Pyrexia	3 (1)	2 (2)
Respiratory failure	3 (1)	1 (1)
Gastrointestinal hemorrhage	3 (1)	1 (1)
Encephalitis cytomegalovirus	3 (1)	1 (1)
Anemia	3 (1)	0
Abdominal pain	3 (1)	0
Febrile neutropenia	2 (1)	4 (3)
Neutropenia	0	3 (3)

Source: adae.xpt; software, R.
[1] Coded as MedDRA preferred term.
Abbreviations: IAT, investigator-assigned treatment; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in group; n, number of subjects with adverse event

TESAEs considered related to study-assigned treatment were more common in the IAT group (15%) than in the maribavir group (5%). The main contributors to this difference between the two treatment groups were the SAEs related to the blood and lymphatic system disorders and renal and urinary disorders. Under the blood and lymphatic system disorders there were 6 (5%) subjects in the IAT group (all of them treated with ganciclovir or valganciclovir) who had SAEs considered related to study drug (febrile neutropenia, 4; neutropenia, 2). None of the subjects in the maribavir group had blood and lymphatic system disorders SAEs considered related to study drug. Under the renal and urinary disorders there were 5 (4%) subjects in the IAT group who were treated with foscarnet and had SAEs considered related to study drug (acute kidney injury, 4; renal impairment, 1). In the maribavir group there were three subjects (1%) who had SAEs considered related to study drug (all 3 with acute kidney injury).

7.6.1.4. Dropouts and/or Discontinuations Due to Adverse Events, Trial 303

A higher proportion of subjects in the IAT group (32%, 37 subjects) had TEAEs leading to discontinuation of study drug compared to the maribavir group (13%, 31 subjects). The difference between the two groups was mainly driven by discontinuations due to AEs in the blood and lymphatic system disorders and the renal and urinary disorders SOCs. Blood dyscrasias in the SOC of blood and lymphatic system disorders were the cause for discontinuation for 13 (11%) subjects in the IAT group, with neutropenia the most common AE leading to treatment discontinuation (11 subjects). All of these hematologic AEs occurred in subjects treated with ganciclovir/valganciclovir.

With regards to AEs leading to drug discontinuation under the SOC of renal and urinary disorders, there were 11 (10%) subjects in the IAT group who discontinued treatment due to AEs. Acute kidney injury occurred in 6 subjects and it was the most common AE among the renal and urinary disorders. None of the subjects in the maribavir group discontinued treatment

for TEAEs in the SOC of renal and urinary disorders. A summary of the TEAEs leading to drug discontinuation by SOC and preferred term are summarized in Table 41.

Table 41. Adverse Events Leading to Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial 303

System Organ Class Preferred Term	Maribavir N=234 n (%)	IAT N=116 n (%)	Risk Difference Between Maribavir and IAT (95% CI)
Blood and lymphatic system disorders	0	13 (11.2)	-11.2 (-16.9, -5.5)
Anemia	0	2 (1.7)	-1.7 (-4.1, 0.6)
Leukopenia	0	3 (2.6)	-2.6 (-5.5, 0.3)
Thrombocytopenia	0	4 (3.4)	-3.4 (-6.8, -0.1)
Neutropenia	0	11 (9.5)	-9.5 (-14.8, -4.2)
Gastrointestinal disorders	4 (1.7)	3 (2.6)	-0.9 (-4.2, 2.5)
Diarrhea	2 (0.9)	1 (0.9)	-0.0 (-2.1, 2.0)
Nausea	2 (0.9)	1 (0.9)	-0.0 (-2.1, 2.0)
Vomiting	1 (0.4)	1 (0.9)	-0.4 (-2.3, 1.4)
General disorders and administration site conditions	2 (0.9)	1 (0.9)	-0.0 (-2.1, 2.0)
General physical health deterioration	1 (0.4)	0	0.4 (-0.4, 1.3)
Pyrexia	1 (0.4)	0	0.4 (-0.4, 1.3)
Oedema peripheral	0	1 (0.9)	-0.9 (-2.5, 0.8)
Hepatobiliary disorders	1 (0.4)	1 (0.9)	-0.4 (-2.3, 1.4)
Hepatic failure	1 (0.4)	0	0.4 (-0.4, 1.3)
Hyperbilirubinemia	1 (0.4)	0	0.4 (-0.4, 1.3)
Cholecystitis	0	1 (0.9)	-0.9 (-2.5, 0.8)
Infections and infestations	17 (7.3)	8 (6.9)	0.4 (-5.3, 6.1)
Cytomegalovirus infection	7 (3.0)	1 (0.9)	2.1 (-0.6, 4.9)
Cytomegalovirus infection reactivation	2 (0.9)	0	0.9 (-0.3, 2.0)
Cytomegalovirus syndrome	1 (0.4)	0	0.4 (-0.4, 1.3)
Pulmonary tuberculosis	1 (0.4)	0	0.4 (-0.4, 1.3)
Septic shock	1 (0.4)	0	0.4 (-0.4, 1.3)
Cytomegalovirus viraemia	4 (1.7)	2 (1.7)	-0.0 (-2.9, 2.9)
Encephalitis cytomegalovirus	2 (0.9)	1 (0.9)	-0.0 (-2.1, 2.0)
BK virus infection	0	1 (0.9)	-0.9 (-2.5, 0.8)
Cytomegalovirus chorioretinitis	0	1 (0.9)	-0.9 (-2.5, 0.8)
Encephalitis viral	0	1 (0.9)	-0.9 (-2.5, 0.8)
Viral hemorrhagic cystitis	0	1 (0.9)	-0.9 (-2.5, 0.8)
Investigations	1 (0.4)	3 (2.6)	-2.2 (-5.2, 0.8)
Hepatic enzyme increased	1 (0.4)	0	0.4 (-0.4, 1.3)
Blood creatinine increased	0	1 (0.9)	-0.9 (-2.5, 0.8)
Weight decreased	0	1 (0.9)	-0.9 (-2.5, 0.8)
White blood cell count decreased	0	1 (0.9)	-0.9 (-2.5, 0.8)
Musculoskeletal and connective tissue disorders	1 (0.4)	0	0.4 (-0.4, 1.3)
Arthralgia	1 (0.4)	0	0.4 (-0.4, 1.3)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	2 (0.9)	2 (1.7)	-0.9 (-3.5, 1.8)
Acute lymphocytic leukemia recurrent	2 (0.9)	0	0.9 (-0.3, 2.0)
Acute myeloid leukemia recurrent	0	1 (0.9)	-0.9 (-2.5, 0.8)
Leukemia recurrent	0	1 (0.9)	-0.9 (-2.5, 0.8)
Nervous system disorders	3 (1.3)	0	1.3 (-0.2, 2.7)
Dysgeusia	2 (0.9)	0	0.9 (-0.3, 2.0)
Headache	1 (0.4)	0	0.4 (-0.4, 1.3)

System Organ Class Preferred Term	Maribavir N=234 n (%)	IAT N=116 n (%)	Risk Difference Between Maribavir and IAT (95% CI)
Psychiatric disorders	1 (0.4)	1 (0.9)	-0.4 (-2.3, 1.4)
Mental status changes	1 (0.4)	0	0.4 (-0.4, 1.3)
Delirium	0	1 (0.9)	-0.9 (-2.5, 0.8)
Renal and urinary disorders	0	11 (9.5)	-9.5 (-14.8, -4.2)
Nephropathy toxic	0	1 (0.9)	-0.9 (-2.5, 0.8)
Proteinuria	0	1 (0.9)	-0.9 (-2.5, 0.8)
Renal failure	0	2 (1.7)	-1.7 (-4.1, 0.6)
Renal impairment	0	2 (1.7)	-1.7 (-4.1, 0.6)
Acute kidney injury	0	6 (5.2)	-5.2 (-9.2, -1.1)
Respiratory, thoracic, and mediastinal disorders	3 (1.3)	0	1.3 (-0.2, 2.7)
Hypoxia	1 (0.4)	0	0.4 (-0.4, 1.3)
Pneumomediastinum	1 (0.4)	0	0.4 (-0.4, 1.3)
Pulmonary embolism	1 (0.4)	0	0.4 (-0.4, 1.3)
Respiratory failure	1 (0.4)	0	0.4 (-0.4, 1.3)

Source: adae.xpt; software, R.
Treatment-emergent adverse events defined as an AE that had a start date on or after the first dose of study-assigned treatment or that had a start date before the date of first dose of study-assigned treatment but increased in severity after the first dose of study-assigned treatment.
Duration is 8 weeks.
Risk difference column shows difference (with 95% confidence interval) between maribavir 400 mg BID and IAT.
Abbreviations: BID, twice daily; CI, confidence interval; IAT, investigator-assigned treatment; N, number of patients in treatment arm; n, number of patients with adverse event

7.6.1.5. Treatment-Emergent Adverse Events, Trial 303

TEAEs were common in study subjects occurring in 97% of the maribavir-treated subjects and 91% of the IAT-treated subjects. The most common TEAEs occurring in more than 5% of subjects in the maribavir group are summarized in Table 42. Dysgeusia was the most common TEAE reported in 37% of the maribavir-treated subjects and in 3% of the IAT-treated subjects. In fact, dysgeusia together with other reported terms of taste disturbance (ageusia, dysgeusia, hypogeusia and taste disorder) occurred in 46% of subjects in the maribavir group and 4% of subjects in the IAT group.

Other notable differences in the proportion of TEAEs between the two treatment groups were the incidence of neutropenia, increased levels of immunosuppressants, abdominal pain, and CMV viremia. Neutropenia is a known adverse event associated with the use of ganciclovir/ valganciclovir. In Trial 303, neutropenia was the most common TEAE reported in the IAT group. It was reported in 22% of subjects in the IAT group and 9% of subjects in the maribavir group. Drug levels of immunosuppressants were monitored during Trial 303 because in a drug interaction study, maribavir was shown to increase trough concentration of tacrolimus by 57%. In Trial 303, the TEAE of immunosuppressant drug level increased was reported in 9% of subjects in the maribavir group compared to 1% of subjects in the IAT group. Abdominal pain was more common in the maribavir group (8%) compared to the IAT group (3%). CMV viremia or reactivation was also more common in the maribavir group (15% versus 5%) during the on-treatment period, probably due to on-treatment virologic failures due to breakthroughs.

TEAEs that occurred with similar frequency between the maribavir and the IAT groups included nausea (21% versus 22%), diarrhea (19% versus 21%), vomiting (14% versus 16%), anemia (12% in each group), fatigue (12% versus 9%), decreased appetite (8% in each group), dizziness (7% versus 4%), peripheral edema (7% versus 8%), blood creatine increased (6% versus 4%),

and dyspnea (6% versus 7%). Table 42 lists all TEAEs reported in Trial 303 with frequency more than 5% in the maribavir group.

Table 42. Treatment-Emergent Adverse Events (All Grades) Reported in >5% in the Maribavir Treatment Group, Trial 303

Preferred Term	Maribavir N=234 n (%)	IAT N=116 n (%)
Any adverse event	228 (97)	106 (91)
Dysgeusia	87 (37)	4 (3)
Nausea	50 (21)	25 (22)
Diarrhea	44 (19)	24 (21)
Vomiting	33 (14)	19 (16)
Anemia	29 (12)	14 (12)
Fatigue	28 (12)	10 (9)
Pyrexia	24 (10)	17 (15)
CMV viremia	24 (10)	6 (5)
Neutropenia	22 (9)	26 (22)
Immunosuppressant drug level increased	21 (9)	1 (1)
Headache	19 (8)	15 (13)
Abdominal pain	18 (8)	3 (3)
Decreased appetite	18 (8)	9 (8)
Dizziness	17 (7)	5 (4)
Edema peripheral	17 (7)	9 (8)
Blood creatinine increased	13 (6)	5 (4)
Dyspnea	13 (6)	8 (7)
Arthralgia	13 (6)	3 (3)
Cough	13 (6)	7 (6)
CMV infection reactivation	12 (5)	3 (3)

Source: adae.xpt; Software R
Duration of exposure to maribavir was approximately 50% longer than the exposure to the IAT drugs.
Abbreviations: CMV, cytomegalovirus; IAT, investigator-assigned treatment; N, number of subjects in study arm; n, number of subjects with specified adverse event

7.6.1.6. Adverse Events of Special Interest, Trial 303

Immunosuppressant Drug Levels Increased

Clinical drug interaction study showed that maribavir increased the whole blood trough concentration of tacrolimus by 57%. As a result, drug levels of immunosuppressant medications were monitored during Trial 303. The results showed that 21 (9%) subjects in the maribavir group and only one subject in the IAT group had increased immunosuppressant drug levels. Another subject who entered the maribavir rescue arm had also increased immunosuppressant drug levels. Among the 21 subjects in the maribavir who had increased immunosuppressant drug levels, 19 subjects had increases in tacrolimus levels and 2 in sirolimus levels.

The trial was designed to collect immunosuppressant drug trough concentrations at baseline, Week 1, Week 8, and Week 9 of study treatment. As with other clinical laboratory tests, these levels may have been drawn at any time during the study with significant elevations entered as adverse events of “increased immunosuppressive drug levels. It is also noteworthy that the investigator assessment of adverse event causality pertained only to study assigned drugs (maribavir or IAT). Therefore, there is no investigator assessment of relationship between adverse events and increased immunosuppressive drug levels. The most notable differences in adverse events between patients with increased immunosuppressive drug levels compared to

those without increased immunosuppressive drug levels were in gastrointestinal events (nausea [43% vs. 19%]; diarrhea [29% vs. 18%]) and renal events (acute kidney injury [24% vs. 7%], increased creatinine levels [14% vs. 5%]). However, due to the small number of subjects with increased immunosuppressive drug levels and the study deficiencies to monitor and assess the adverse events in association with immunosuppressive drug levels, it is challenging to draw any conclusions. Of note, the drug label emphasizes the need for frequent monitoring of the levels of immunosuppressive drugs that are CYP3A4 and/or P-glycoprotein substrates (including tacrolimus, sirolimus, everolimus, and cyclosporine).

Invasive fungal, bacterial or viral infections

A slightly higher proportion of maribavir-treated subjects had treatment-emergent adverse events of invasive fungal, bacterial or viral infections compared to subjects in the IAT group (24% vs. 19%, respectively). These results should be interpreted with caution and take into consideration the longer exposure to maribavir compared to the IAT drugs.

Graft Versus Host Disease (GVHD)

Twenty-one (19%) maribavir-treated subjects had a treatment-emergent adverse event of new or worsening GVHD compared to 4% of subjects in the IAT group. It should be noted that at baseline the percentage of subjects with acute GVHD was numerically higher in the maribavir-treated subjects compared to the IAT-treated subjects (10% vs. 7%).

7.6.1.7. Laboratory Findings, Trial 303

Hematologic abnormalities are the major laboratory abnormalities usually occur with the use of ganciclovir or valganciclovir. These laboratory abnormalities are also common adverse events of the immunosuppressive medications taken by transplant patients. Renal impairment and electrolyte abnormalities (i.e., hypocalcemia, hypophosphatemia, hyperphosphatemia, hypomagnesemia, and hypokalemia) are the major abnormalities associated with the use of foscarnet, whereas the use of cidofovir is associated with renal impairment and neutropenia. To investigate the effects of these drugs on these abnormalities and possible differences with the use of maribavir, we summarize the laboratory results related to these laboratory parameters in Table 43 and Table 44.

Table 43. Selected Laboratory Abnormalities, Worse Case Reported During the On-Treatment Observation Period, Trial 303

Laboratory Test	Maribavir N=234 n (%)	IAT N=116 n (%)
Neutrophils (cells/µL)		
<500	4 (2)	4 (3)
500 to 750	7 (3)	7 (6)
750 to 1,000	10 (4)	6 (5)
Platelets (cells/µL)		
<25,000	11 (5)	6 (5)
25,000 to 50,000	27 (12)	10 (9)
50,000 to 100,000	41 (18)	20 (17)
Hemoglobin (g/dL)		
<6.5	3 (1)	1 (1)
6.5 to 8.0	34 (15)	23 (20)
8.0 to 9.5	76 (32)	33 (28)
Creatinine (mg/dL)		
>2.5	16 (7)	12 (10)
1.5 to 2.5	78 (33)	29 (25)

Source: ad b.xpt; software, R.
Duration is 8 weeks.
Abbreviations: IAT, Investigator assigned treatment; N, number of subjects with relevant laboratory data; n, number of subjects with abnormality

Table 44. Selected Grade 3 and 4 Laboratory Abnormalities During the On-Treatment Period, Trial 303

Laboratory Test	Maribavir N=234 n (%)	IAT N=116 1. n (%)
Neutrophils decreased		
Grade 3	17 (7)	13 (11)
Grade 4	4 (2)	4 (3)
Hemoglobin decreased		
Grade 3	37 (16)	24 (21)
Grade 4	0	0
Platelets decreased		
Grade 3	27 (12)	10 (9)
Grade 4	11 (5)	6 (5)
Creatinine increased		
Grade 3	6 (3)	2 (2)
Grade 4	0	0
Calcium decreased		
Grade 3	2 (1)	0
Grade 4	0	0
Potassium decreased		
Grade 3	8 (3)	4 (3)
Grade 4	0	0
Phosphate decreased		
Grade 3	12 (5)	6 (5)
Grade 4	0	0
Magnesium decreased		
Grade 3	1 (<1)	0
Grade 4	0	0

Laboratory Test	Maribavir N=234 n (%)	IAT N=116 1. n (%)
Alanine aminotransferase increased		
Grade 3	7 (3)	0
Grade 4	1 (<1)	0
Bilirubin increased		
Grade 3	4 (2)	1 (1)
Grade 4	1 (<1)	0

Source: ad b.xpt; Software R
Abbreviations: IAT, investigator-assigned treatment; N, number of subjects in study arm; n, number of subjects within specified category

There were no appreciable differences in decreased magnesium, phosphate, potassium, or calcium, or in increased bilirubin or creatinine levels. Slight differences were noted in Grade 3 decreased neutrophil levels (maribavir 7%, IAT 11%) but not in the most severe form of neutropenia (Grade 4, neutrophils <500 cells/µL). Grade 3 decreased hemoglobin levels were also numerically higher in the IAT arm (21%) compared to the maribavir arm (16%) but no cases of Grade 4 decreased hemoglobin were observed in either arm. Numerically higher Grade 3 levels decreased platelets were noted in the maribavir arm compared to IAT arm (12% versus 9%, respectively) and in increased alanine aminotransferase (3% versus 0% in maribavir and IAT arms, respectively). Overall, the differences between the groups were minimal and were not to the degree expected with the use of ganciclovir/valganciclovir, foscarnet, and cidofovir.

To further explore potential differences in laboratory abnormalities between maribavir and IAT groups, we compared the shifts of 3 or 4 grades in the previously selected laboratory abnormalities. The results are shown in Table 45.

Table 45. Shifts of 3 or 4 Grades From Baseline During the On-Treatment Period in Selected Laboratory Abnormalities, Trial 303

Laboratory Test	Maribavir N=234 n (%)	IAT N=116 n (%)
Neutrophils decreased		
Three-grade shift	10 (4)	11 (9)
Four-grade shift	2 (1)	0
Hemoglobin decreased		
Three-grade shift	0	2 (2)
Four-grade shift	0	0
Platelets decreased		
Three-grade shift	2 (1)	1 (1)
Four-grade shift	2 (1)	0
Creatinine increased		
Three-grade shift	3 (1)	0
Four-grade shift	0	0
Calcium decreased		
Three-grade shift	1 (<1)	0
Four-grade shift	0	0
Potassium decreased		
Three-grade shift	5 (2)	4 (3)
Four-grade shift	0	0
Phosphate decreased		
Three-grade shift	8 (3)	4 (3)
Four-grade shift	0	0
Magnesium decreased		
Three-grade shift	1 (<1)	0
Four-grade shift	0	0
Alanine aminotransferase increased		
Three-grade shift	1 (<1)	0
Four-grade shift	1 (<1)	0
Bilirubin increased		
Three-grade shift	3 (1)	0
Four-grade shift	0	0

Source: ad b.xpt; Software R
Abbreviation: IAT, investigator-assigned treatment; N, number of subjects in study arm; n, number of subjects with specified shift

No major differences were noted between the two treatment groups in shifts of 3 or 4 grades in the selected laboratory abnormalities shown in Table 45. The only minor differences noted were in decreased neutrophil counts and hemoglobin levels. Shifts of 3 grades in decreased neutrophils were noted in 10 (4%) subjects in the maribavir group and 11 (9%) subjects in the IAT group. There was only one subject with a shift of 4 grades and that subject was in the maribavir group. Only two subjects in the IAT group and none in the maribavir group had a 3-grade shift in decreased hemoglobin. There were no subjects with a shift of 4 grades in decreased hemoglobin levels in either arm.

7.6.2. Safety Findings and Concerns, Trial 202

7.6.2.1. Overall Treatment-Emergent Adverse Event Summary, Trial 202

The overview of the treatment-emergent adverse events for the Phase 2 Trial 202 is summarized in Table 46. No appreciable differences were noted among the three maribavir treatment groups.

However, the overall proportion of subjects with SAEs, SAEs with fatal outcome, AEs leading to discontinuation or modification of study drug were higher than those observed in the maribavir group of the Phase 3 trial (Trial 303), a trial with similar population to this trial.

Table 46. Overview of Treatment-Emergent Adverse Events, Trial 202

Event Category	Maribavir 400 mg BID N=40 n (%)	Maribavir 800 mg BID N=40 n (%)	Maribavir 1,200 mg BID N=40 n (%)	Maribavir All Doses N=120 n (%)
Subjects with any treatment-emergent AE	40 (100)	40 (100)	40 (100)	120 (100)
Subjects with severe AEs	16 (40)	18 (45)	14 (35)	48 (40)
Subjects with maximal AEs	8 (20)	8 (20)	11 (28)	27 (23)
SAEs	28 (70)	27 (68)	26 (65)	81 (68)
SAEs with an outcome of death	10 (25)	12 (30)	10 (25)	32 (27)
Subjects with AEs leading to discontinuation of study drug	11 (28)	17 (43)	13 (33)	41 (34)
Subjects with AEs leading to dosage modification of study drug	6 (15)	5 (13)	9 (23)	15 (13)
Subjects with AEs leading to interruption of study drug	6 (15)	5 (13)	9 (23)	20 (17)

Source: adae.xpt; software, R.
Abbreviations: AE, adverse event; BID, twice daily; SAE, serious adverse event; N, number of subjects in group; n, number of subjects with at least one event

7.6.2.2. Deaths, Trial 202

A total of 32 (27%) subjects died in Trial 202. No difference was observed in all-cause mortality among the three maribavir treatment groups; 10 (25%), 12 (30%), and 10 (25%) subjects in the 400 mg BID, 800 mg BID, and 1,200 mg BID groups, respectively. Although the subjects enrolled in Trials 202 and 303 were similar (resistant/refractory and tissue-invasive CMV disease), the overall all-cause mortality in this Phase 2 trial was higher than the all-cause mortality observed in the maribavir group of the Phase 3 Trial 303 (11%). However, it should be noted that Trial 202 had a longer duration (up to 24 weeks treatment and 12 weeks of follow-up) than the Phase 3 Trial 303 (up to 8 weeks of treatment and 12 weeks follow-up). The median exposure to maribavir in was 75 days in Trial 202 and 57 days in Trial 303.

There was no consistent pattern of SAEs with an outcome of death within each group or among the three groups. Two of the 32 subjects reported more than 1 SAE with outcome of death. Most of the SAEs were reported in one subject each. No SAE was reported in more than two subjects in each group. The most common SAEs with an outcome of death were sepsis (five cases [maribavir 400 mg BID two cases, maribavir 800 mg BID one case, and maribavir 1,200 mg BID two cases]), multi-organ failure (four cases), renal impairment (three cases), acute graft versus host disease (two cases), acute respiratory distress syndrome (two cases), leukemia recurrent (two cases), pneumonia (two cases), and pneumonia cytomegaloviral (two cases).

Only one subject in the 800 mg BID group had an SAE with fatal outcome that was considered by the Investigator to be possibly related to study drug (see Section III.17.2.1 for a brief description of this case. Overall, the analysis of SAEs with a fatal outcome does not reveal any specific risks associated with study drug. The causes of deaths for the 32 subjects in Trial 202 are summarized in Table 127.

7.6.2.3. Serious Adverse Events, Trial 202

A total of 81 subjects (68%) had one or more TESAE. No difference was noted in the proportion of subjects with treatment-emergent SAEs among the maribavir treatment groups. Twenty-eight (70%) subjects in the 400 mg BID experienced at least one TESAE, 27 (68%) subjects in the 800 mg BID group, and 26 (65%) in the 1,200 mg BID group. The most common TESAE was CMV infection (12% overall; 8% in the 400 mg BID group, 13% in the 800 mg BID, and 15% in the 1,200 mg BID group). The next most common TESAEs were nausea (6%), renal impairment (6%), and sepsis (5%) with no obvious dose-dependent trend. Table 47 summarizes the most common TESAEs.

Table 47. Treatment-Emergent Serious Adverse Events Reported by 3 or More Subjects in the Combined Maribavir Groups

Treatment-Emergent Serious Adverse Event (TESAE)	Maribavir 400 mg BID N=40 n (%)	Maribavir 400 mg BID N=40 n (%)	Maribavir 1,200 mg BID N=40 n (%)	Maribavir All Doses N=120 n (%)
Subjects with any TESAE	28 (70)	27 (68)	26 (65)	81 (68)
Cytomegalovirus infection	3 (8)	5 (13)	6 (15)	14 (12)
Nausea	1 (3)	3 (8)	3 (8)	7 (6)
Renal impairment	2 (5)	3 (8)	2 (5)	7 (6)
Sepsis	2 (5)	3 (8)	1 (3)	6 (5)
Anemia	4 (10)	0	0	4 (3)
Dehydration	1 (3)	1 (3)	2 (5)	4 (3)
Lung transplant rejection	2 (5)	1 (3)	1 (3)	4 (3)
Multi-organ failure	1 (3)	1 (3)	2 (5)	4 (3)
Pneumonia	1 (3)	2 (5)	1 (3)	4 (3)
Bacteremia	1 (3)	2 (5)	0	3 (3)
Clostridium difficile infection	2 (5)	0	1 (3)	3 (3)
Diarrhea	0	2 (5)	1 (3)	3 (3)
Failure to thrive	1 (3)	1 (3)	1 (3)	3 (3)
Pneumonia cytomegaloviral	1 (3)	0	2 (5)	3 (3)
Pyrexia	2 (5)	1 (3)	0	3 (3)
Respiratory failure	0	0	3 (8)	3 (3)

Source: adae.xpt; Software R
Abbreviation: BID, twice daily; N, number of subjects in group; n, number of subjects with indicated TESAE; TESAE, treatment-emergent serious adverse event

Twenty subjects had at least one TESAE that was considered by investigators as related to study drug: 8 subjects (20%) in the 400 mg BID group, 7 subjects (18%) in the 800 mg BID group, and 5 subjects (13%) in the 1,200 mg BID group. The most common reported TESAEs considered related to study drug were cytomegalovirus infection and nausea reported in 5 subjects in the combined maribavir groups, followed by anemia which was reported in two subjects. All other related TESAEs were reported by one subject each.

7.6.2.4. Dropouts and/or Discontinuations Due to Adverse Events, Trial 202

A total of 41 (34%) subjects in Trial 202 were discontinued from maribavir due to AEs. The highest rate of discontinuation occurred in the 800 mg BID group (43%, 17 subjects), followed by the 1,200 mg BID group (33%, 13 subjects) and the 400 mg BID group (28%, 11 subjects). Adverse events in the SOC of Infections and infestations were the leading cause of discontinuations (24 subjects in combined maribavir groups), with cytomegalovirus infection

being responsible for 17 of the 24 (4 subjects in the 400 mg BID group, 8 in the 800 mg BID group, and 5 in the 1,200 mg BID group). The next most common AE leading to study drug discontinuation was nausea which occurred in three subjects (one subject in each treatment group). encephalopathy, multi-organ failure, and renal impairment were reported in two subjects each. All other AEs leading to discontinuation occurred in one subject each. A summary of the TEAEs leading to drug discontinuation by SOC and preferred term is shown in Table 48.

Table 48. Adverse Events Leading to Discontinuation by System Organ Class and Preferred Term, Intent-to-Treat Safety Population, Trial 202

System Organ Class Preferred Term	Maribavir 400 mg BID N=40 n (%)	Maribavir 800 mg BID N=40 n (%)	Maribavir 1,200 mg BID N=40 n (%)	Maribavir All Doses N=120 n (%)
Blood and lymphatic system disorders	0	0	1 (3)	1 (1)
Anemia	0	0	1 (3)	1 (1)
Gastrointestinal disorders	1 (3)	2 (5)	1 (3)	4 (3)
Nausea	1 (3)	1 (3)	1 (3)	3 (3)
Diarrhea	0	1 (3)	0	1 (1)
Dysphagia	0	1 (3)	0	1 (1)
Vomiting	0	1 (3)	0	1 (1)
General disorders and administration site conditions	1 (3)	0	1 (3)	2 (2)
Multiorgan failure	1 (3)	0	1 (3)	2 (2)
Infections and infestations	7 (18)	11 (28)	6 (15)	24 (20)
Cytomegalovirus infection	4 (10)	8 (20)	5 (13)	17 (14)
Cytomegalovirus gastroenteritis	1 (3)	0	0	1 (1)
Pneumonia cytomegaloviral	1 (3)	0	0	1 (01)
Sepsis	1 (3)	0	0	1 (1)
Bacteremia	0	1 (3)	0	1 (1)
Cytomegalovirus chorioretinitis	0	1 (3)	0	1 (1)
Encephalitis cytomegalovirus	0	1 (3)	0	1 (1)
Pneumocystis jirovecii pneumonia	0	0	1 (3)	1 (1)
Investigations	0	1 (3)	1 (3)	2 (2)
Blood creatinine increased	0	1 (3)	0	1 (1)
Immunosuppressant drug level increased	0	0	1 (3)	1 (1)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	0	1 (3)	0	1 (1)
Post-transplant lymphoproliferative disorder	0	1 (3)	0	1 (1)
Nervous system disorders	1 (3)	1 (3)	2 (5)	4 (3)
Encephalopathy	1 (3)	1 (3)	0	2 (2)
Clonus	0	0	1 (3)	1 (1)
Dysgeusia	0	0	1 (3)	1 (1)
Renal and urinary disorders	1 (3)	1 (3)	0	2 (2)
Renal impairment	1 (3)	1 (3)	0	2 (2)

Source: adae.xpt; software, R.
Treatment-emergent adverse events defined as an AE that had a start date on or after the first dose of study-assigned treatment or that had a start date before the date of first dose of study-assigned treatment but increased in severity after the first dose of study-assigned treatment.
Duration is 24 weeks.
Abbreviations: AE, adverse event; BID, twice daily; N, number of patients in treatment arm; n, number of patients with adverse event

7.6.2.5. Treatment-Emergent Adverse Events, Trial 202

A total of 120 subjects received at least one dose of study drug. All patients experienced at least one treatment-emergent adverse event. This is not unexpected considering the underlying disease

and the prolonged duration of treatment (the overall median exposure to study drug was 75 days). Approximately 85% of the TEAEs were mild or moderate in severity in all three treatment groups. In general, there were no substantial differences in safety among the treatment groups, as well as no clear dose-response for any specific adverse event, although AEs of dysgeusia, anemia, renal impairment, hypokalemia, and increased immunosuppressant drug levels were numerically higher in the 1,200 mg maribavir group.

The most common TEAE was dysgeusia, reported in 65% of the subjects (400 mg BID 60%, 800 mg BID 63%, and 1,200 mg BID 73%). Gastrointestinal disorders were also frequently reported. Nausea was reported in 34% of the study subjects, vomiting in 29%, and diarrhea in 23%. CMV infection was the next most common TEAE, reported in 23% for the overall maribavir group. Renal impairment was reported by 16% of subjects and the TEAE of immunosuppressant drug level increased was reported in 10%. Overall, the TEAE profile of maribavir reported in Trial 202 was similar to that observed in Trial 203. The TEAEs reported in at least 10% of the subjects is shown in Table 49.

Table 49. Treatment-Emergent AEs (All Grades) Reported in ≥10% of Subjects in the Overall Maribavir Group (Safety Population), Trial 202

Preferred Term	Maribavir 400 mg BID N=40 n (%)	Maribavir 800 mg BID N=40 n (%)	Maribavir 1,200 mg BID N=40 n (%)	Maribavir All Doses N=120 n (%)
Patients with any AE	40 (100)	40 (100)	40 (100)	120 (100)
Dysgeusia	24 (60)	25 (63)	29 (73)	78 (65)
Nausea	15 (38)	12 (30)	14 (35)	41 (34)
Vomiting	11 (28)	13 (33)	11 (28)	35 (29)
CMV infection	6 (15)	12 (30)	10 (25)	28(23)
Diarrhea	5 (13)	13 (33)	10 (25)	28(23)
Fatigue	8 (20)	10 (25)	7 (18)	25 (21)
Anemia	7 (18)	7 (18)	10 (25)	24 (20)
Edema peripheral	11 (28)	6 (15)	6 (15)	23 (19)
Headache	9 (23)	4 (10)	6 (15)	19 (16)
Renal impairment	3 (8)	7 (18)	9 (23)	19 (16)
Rash	7 (18)	6 (15)	3 (8)	16 (13)
Constipation	5 (13)	5 (13)	5 (13)	15 (13)
Pneumonia	6 (15)	4 (10)	5 (13)	15 (13)
Pyrexia	6 (15)	6 (15)	3 (8)	15 (13)
Cough	5 (13)	6 (15)	2 (5)	13 (11)
Decreased appetite	3 (8)	5 (13)	4 (10)	12 (10)
Dehydration	5 (13)	4 (10)	3 (8)	12 (10)
Hypokalemia	2 (5)	4 (10)	6 (15)	12 (10)
Immunosuppressant drug level increased	4 (10)	2 (5)	6 (15)	12 (10)
Urinary tract infection	6 (15)	3 (8)	3 (8)	12 (10)

Source: adae.xpt; Software R.
Abbreviations: AE, adverse event; BID, twice daily; CMV, cytomegalovirus; N, number of subjects in group; n, number of subjects with indicated AE

7.6.2.6. Laboratory Findings, Trial 202

There were no appreciable trends in laboratory abnormalities across the three maribavir dose groups. Selected laboratory parameters of interest are summarized in Table 50. There were only three cases of neutropenia <500 cells/µL, one in each group. There was also 1 report with neutrophils between 500 t0 750 cells/µL in the 400 mg BID group, and four cases between 750

to 1,000 cells/µL (one each in the 400 mg and 1,200 mg BID groups and 2 in the 800 mg BID group.

Decreased platelet count <25,000 cells/µL was reported in total of 14 (12%) cases (4 in the 400 mg BID, 8 in the 800 mg BID and 2 in the 1,200 mg BID group). There was only one report with hemoglobin <6.5 g/dL in the 800 mg BID group. A somewhat higher number of reports with creatinine levels >2.5 mg/dL occurred in the 1,200 mg BID group (12 subjects, 30%), compared to the other two treatment groups (10% in the 400 mg BID and 13% in the 800 mg BID group).

Table 50. Selected Laboratory Abnormalities, Worse-Case Reported During Treatment Period, Trial 202

Laboratory Test	Maribavir 400 mg BID N=40 n (%)	Maribavir 800 mg BID N=40 n (%)	Maribavir 1,200 mg BID N=40 n (%)	Maribavir All Doses N=120 n (%)
Neutrophils (cells/µL)				
<500	1 (3)	1 (3)	1 (3)	3 (3)
500 to 750	1 (3)	0	0	1 (1)
750 to 1,000	1 (3)	2 (5)	1 (3)	4 (3)
Platelets (cells/µL)				
<25,000	4 (10)	8 (20)	2 (5)	14 (12)
25,000 to 50,000	5 (13)	6 (15)	4 (10)	15 (13)
50,000 to 100,000	8 (20)	3 (8)	4 (10)	15 (13)
Hemoglobin (g/dL)				
<6.5	0	1 (3)	0	1 (1)
6.5 to 8.0	6 (15)	14 (35)	10 (25)	30 (25)
8.0 to 9.5	20 (50)	13 (33)	21 (53)	54 (45)
Creatinine (mg/dL)				
>2.5	4 (10)	5 (13)	12 (30)	21 (18)
1.5 to 2.5	12 (30)	11 (28)	12 (30)	35 (29)

Source: ad b.xpt; software, R.
Duration is 24 weeks.
Abbreviations: BID, twice daily; N, number of subjects with relevant laboratory data; n, number of subjects with abnormality

Because many transplant subjects have severe laboratory abnormalities at baseline, the best approach to identify new laboratory abnormalities possibly related to the investigational drug is to compare the shifts in laboratory values at specific time with the baseline values. None of the subjects had 3 or 4 shift grades in decreased hemoglobin or increased creatinine levels. There was one subject with 3 grades shift in decreased platelet values and one with 4 grades shift, both of them in the 400 mg BID group. A total of 5 (4%) subjects had 3 grades shift in decreased neutrophil counts (one subject in the 400 mg BID, two subjects in the 800 mg BID, and two subjects in the 1,200 mg BID groups). These results are shown in Table 51.

Table 51. Shifts of 3 or 4 Grades for Neutrophils, Hemoglobin, Platelets, and Creatinine, Trial 202

Laboratory Test	Maribavir 400 mg BID N=40 n (%)	Maribavir 800 mg BID N=40 n (%)	Maribavir 1,200 mg BID N=40 n (%)	Maribavir All Doses N=120 n (%)
Neutrophils decreased				
Three-grade shift	1 (3)	2 (5)	2 (5)	5 (4)
Four-grade shift	0	0	0	0

Laboratory Test	Maribavir 400 mg BID N=40 n (%)	Maribavir 800 mg BID N=40 n (%)	Maribavir 1,200 mg BID N=40 n (%)	Maribavir All Doses N=120 n (%)
Hemoglobin decreased				
Three-grade shift	0	0	0	0
Four-grade shift	0	0	0	0
Platelets decreased				
Three-grade shift	1 (3)	0	0	1 (1)
Four-grade shift	1 (3)	0	0	1 (1)
Creatinine increased				
Three-grade shift	0	0	0	0
Four-grade shift	0	0	0	0

Source: ad b.xpt; software, R.
Abbreviation: BID, twice daily; N, number of subjects with relevant laboratory data; n, number of subjects with indicated shift

7.6.3. Safety Findings and Concerns, Trial 203

7.6.3.1. Overall Adverse Event Summary, Trial 203

The treatment-emergent adverse events for the Phase 2 trial, 203, are summarized in Table 52. No appreciable differences were noted among the three maribavir treatment groups. In addition, no notable differences were observed between the overall maribavir group and the valganciclovir with regards to SAEs, severe AEs or AEs with maximal severity, SAEs with fatal outcome or AEs with interruption of study drug. However, the proportion of subjects with at least one TEAE was higher in the overall maribavir group compared to the valganciclovir group (97% versus 85%) probably driven by the high proportion of maribavir-treated subjects who experienced dysgeusia. The proportion of subjects with SAEs and AEs leading to discontinuation of study drug were also higher in the overall maribavir-treated subjects compared to the valganciclovir-treated subjects (SAEs: 44% versus 33%, AEs leading to discontinuation of study drug: 23% versus 13%). On the other hand, a higher proportion of subjects treated with valganciclovir had dose adjustment compared to subjects treated with maribavir (48% versus 8%). A possible explanation for some of the differences could be attributed to the longer exposure to maribavir compared to valganciclovir. The median duration of exposure to maribavir was 45 days and to valganciclovir was 33 days. No significant difference in the mean duration of exposure was observed between the maribavir and valganciclovir treated subjects (49 versus 45 days).

Table 52. Overview of Treatment-Emergent Adverse Events, Trial 203

Event Category	Maribavir 400 mg BID N=40 n (%)	Maribavir 800 mg BID N=40 n (%)	Maribavir 1,200 mg BID N=39 n (%)	Maribavir All Doses N=119 n (%)	Valganciclovir N=40 n (%)
Subjects with any treatment-emergent AE[1]	39 (98)	38 (95)	39 (100)	116 (97)	34 (85)
Subjects with severe AEs	11 (28)	14 (35)	13 (33)	38 (32)	11 (28)
Subjects with maximal AEs[2]	3 (8)	2 (5)	4 (10)	9 (8)	5 (13)
Subjects with SAEs	16 (40)	17(43)	19 (49)	52 (44)	13 (33)
Subjects with SAEs and fatal outcome	2 (5)	1 (3)	3 (8)	6 (5)	3 (8)

Event Category	Maribavir 400 mg BID N=40 n (%)	Maribavir 800 mg BID N=40 n (%)	Maribavir 1,200 mg BID N=39 n (%)	Maribavir All Doses N=119 n (%)	Valganciclovir N=40 n (%)
Subjects with AEs leading to discontinuation of study drug	12 (30)	5 (13)	10 (26)	27 (23)	5 (13)
Subjects with AEs leading to interruption of study drug	3 (8)	1 (3)	6 (15)	10 (8)	2 (5)
Subjects with dose adjustment	2 (5)	2 (5)	6 (15)	10 (8)	19 (48)

Source: adae.xpt; Software R.
[1] Includes treatment-emergent AE defined as an AE that had start date on or after the first dose of study-assigned treatment or that had a start date before the date of the first dose of study-assigned treatment but increased in severity after the first dose of study assigned treatment.
Duration is 12 weeks.
[2] In this trial, the intensity of adverse events was graded as mild (Grade 1), moderate (Grade 2), severe (Grade 3), and maximal, i.e., life-threatening or disabling (Grade 4).
Abbreviations: AE, adverse event; BID, twice daily; N, number of subjects in group; n, number of subjects with at least one event; SAE, serious adverse event

7.6.3.2. Deaths, Trial 203

There were 9 deaths in this trial: 6 (5%) in the overall maribavir group and 3 (8%) in the valganciclovir group. The deaths in the maribavir-treated subjects were 2 (5%) in the 400 mg BID group, 1 (3%) in the 800 mg BID group, and 3 (8%) in the 1,200 mg BID group. The deaths in this trial were lower than those observed in the Phase 3 Trial 303 (11%) and in the Phase 2 Trial 202 (27%). This is not unexpected given that subjects in this trial were less sick (subjects with asymptomatic CMV viremia) compared to the subjects in the other two trials (which included subjects in the trials with CMV disease, resistant/refractory to ganciclovir, valganciclovir, foscarnet or cidofovir).

There was no consistent pattern of SAEs with an outcome of death in this trial and none of the SAEs with an outcome of death was considered by investigators as related to study drug (maribavir or valganciclovir). In some cases, more than one SAE was reported with an outcome of death for an individual subject. Only two SAEs (sepsis and multi-organ failure) were reported in more than one subject. Sepsis with an outcome of death was reported in three subjects; two subjects in the overall maribavir group (one subject in the 400 mg BID group and one subject in the 1,200 mg BID group) and one subject treated with valganciclovir. Multi-organ failure was reported in two subjects: one subject in the 400 mg BID maribavir group and one subject in the valganciclovir group. Please refer to a list with the nine deaths, six maribavir-treated subjects and 3 valganciclovir-treated subjects, who had SAEs with an outcome of death is provided in Table 129.

7.6.3.3. Serious Adverse Events, Trial 203

Non-fatal TESAEs were reported in 44% of subjects in the overall maribavir group and 33% in the valganciclovir group. No significant difference was noted in the proportion of subjects with TESAEs among the 3 maribavir treatment groups (40% in the 400 mg BID group, 43% in the 800 mg BID group, and 49% in the 1,200 mg BID group). Acute graft versus host disease, diarrhea, and renal failure were the only SAEs that were reported in three subjects in the overall

maribavir group. Sepsis was the only SAE reported in 3 (8%) subjects in the valganciclovir subjects. Table 53 summarizes the TESAEs reported by at least two subjects in any treatment group.

Table 53. Treatment-Emergent Serious Adverse Events Reported by 2 or More Subjects in Any Treatment Group (Trial 203)

Preferred Term	Maribavir 400 mg BID N=40 n (%)	Maribavir 800 mg BID N=40 n (%)	Maribavir 1,200 mg BID N=39 n (%)	Maribavir All Doses N=119 n (%)	Valganciclovir N=40 n (%)
Number of subjects with any TESAE	16 (40)	17 (43)	19 (49)	52 (44)	13 (33)
Acute graft-vs.-host disease	0	0	3 (8)	3 (3)	2 (5)
Diarrhea	0	1 (3)	2 (5)	3 (3)	0
Renal failure	2 (5)	0	1 (3)	3 (3)	0
Urinary tract infection	0	2 (5)	1 (3)	3 (3)	0
Cytomegalovirus infection	2 (5)	0	0	2 (2)	1 (3)
Gastroenteritis	2 (5)	0	0	2 (2)	0
Malaise	0	0	2 (5)	2 (2)	0
Sepsis	0	0	2 (5)	2 (2)	1 (3)
Bacterial sepsis	0	0	0	0	3 (8)

Source: adae.xpt; Software R
Abbreviations: BID, twice daily; N, number of subjects in group; n, number of subjects with at least one event; TESAE, treatment-emergent serious adverse event

Twelve maribavir-treated subjects and 1 valganciclovir-treated subject had TESAEs considered by investigators as related to study drug (maribavir or valganciclovir). Diarrhea and decreased appetite were the only TESAEs considered by investigators related to maribavir (reported by two subjects). All other TESAEs were reported by only one subject. The only TESAE considered by the Investigator as related to valganciclovir was a case of CMV infection. A summary of TESAEs by SOC and preferred term considered by investigators related to study drug is provided in Table 54.

Table 54. Treatment-Emergent Serious Adverse Events Assessed by Investigator as Treatment-Related by System Organ Class and Preferred Term, Intent-to-Treat Safety Population, Trial 203

System Organ Class Preferred Term	Maribavir 400 mg BID N=40 n (%)	Maribavir 800 mg BID N=40 n (%)	Maribavir 1,200 mg BID N=39 n (%)	Maribavir All Doses N=119 n (%)	Valganciclovir N=40 n (%)
Gastrointestinal disorders	0	0	4 (10)	4 (3)	0
Diarrhea	0	0	2 (5)	2 (2)	0
Gastrointestinal toxicity	0	0	1 (3)	1 (1)	0
Vomiting	0	0	1 (3)	1 (1)	0
Infections and infestations	1 (3)	0	1 (3)	2 (1)	1 (3)
Oral herpes	0	0	1 (3)	1 (1)	0
Cytomegalovirus infection	1 (3)	0	0	1 (1)	1 (3)
Investigations	0	0	1 (3)	1 (1)	0
Immunosuppressant drug level increased	0	0	1 (3)	1 (1)	0
Metabolism and nutrition disorders	1 (3)	1 (3)	1 (3)	3 (3)	0
Decreased appetite	1 (3)	0	1 (3)	2 (2)	0
Dehydration	0	1 (3)	0	1 (1)	0

System Organ Class Preferred Term	Maribavir 400 mg BID N=40 n (%)	Maribavir 800 mg BID N=40 n (%)	Maribavir 1,200 mg BID N=39 n (%)	Maribavir All Doses N=119 n (%)	Valganciclovir N=40 n (%)
Nervous system disorders	0	0	1 (3)	1 (1)	0
Toxic encephalopathy	0	0	1 (3)	1 (1)	0
Psychiatric disorders	1 (3)	0	0	1 (1)	0
Confusional state	1 (3)	0	0	1 (1)	0

Source: adae.xpt; software, R.
Treatment-emergent adverse events defined as an AE that had a start date on or after the first dose of study-assigned treatment or that had a start date before the date of first dose of study-assigned treatment but increased in severity after the first dose of study-assigned treatment.
Duration is 12 weeks.
Abbreviations: BID, twice daily; N, number of patients in treatment arm; n, number of patients with adverse event

7.6.3.4. Dropouts and/or Discontinuations Due to Adverse Events, Trial 203

A higher proportion of the overall maribavir-treated subjects (23%, 27 subjects) had TEAEs leading to premature discontinuation of study drug compared to the valganciclovir-treated subjects (13%, 5 subjects). Among the three maribavir treatment groups the highest proportion of subjects who discontinued treatment due to TEAE was observed in the 400 mg BID group (30%, 12 subjects) and the lowest in the 800 mg BID group (13%, 5 subjects). The proportion of subjects who discontinued treatment in the 1,200 mg BID group was 26% (10 subjects).

CMV infection was the leading cause for the discontinuation in the maribavir-treated subjects (it should be noted that based on study protocol, subjects may have prematurely discontinued study drug due to CMV infection or disease requiring alternative treatment). A total of 6 (5%) subjects with CMV infection in the maribavir-treated subjects discontinued treatment (5 subjects in the 400 mg BID group, and 1 in the 1,200 mg BID group). No subjects in the valganciclovir group discontinued treatment due to CMV infection. Nausea, vomiting, decreased appetite, and diarrhea were the next most common TEAEs leading to discontinuation of maribavir, each one reported by two subjects. All other TEAEs leading to discontinuation of maribavir were reported by one subject each. Leukopenia was the only TEAE in the valganciclovir group which was reported by two subjects. All other TEAEs resulting in discontinuation of valganciclovir were reported by one subject. Table 55 summarizes all TEAEs causing discontinuation from study drug in at least two subjects overall.

Table 55. TEAEs Leading to Discontinuation from Study Drug Reported by at Least 2 Subjects Overall, Trial 203

Preferred Term	Maribavir 400 mg BID N=40 n (%)	Maribavir 800 mg BID N=40 n (%)	Maribavir 1,200 mg BID N=39 n (%)	Maribavir All Doses N=119 n (%)	Valganciclovir N=40 n (%)
Number of subjects with any TEAE causing discontinuation from study drug	12 (30)	5 (13)	10 (26)	27 (23)	5 (13)
Cytomegalovirus infection	5 (13)	0	1 (3)	6 (5)	0
Nausea	0	1 (3)	2 (5)	3 (3)	0
Vomiting	1 (3)	0	2 (5)	3 (3)	0
Decreased appetite	1 (3)	0	1 (3)	2 (2)	0
Diarrhea	1 (3)	0	1 (3)	2 (2)	0

Preferred Term	Maribavir 400 mg BID N=40 n (%)	Maribavir 800 mg BID N=40 n (%)	Maribavir 1,200 mg BID N=39 n (%)	Maribavir All Doses N=119 n (%)	Valganciclovir N=40 n (%)
Acute graft-vs.-host disease	0	0	1 (3)	1 (1)	1 (3)
Hepatic enzyme increased	0	1 (3)	0	1 (1)	1 (3)
Leukopenia	0	0	0	0	2 (5)

Source: adae.xpt; Software R
Abbreviations: BID, twice daily; N, number of patients in treatment arm; n, number of patients with adverse event; TEAE, treatment-emergent adverse event

Sixteen of the 27 maribavir-treated subjects with TEAEs causing drug discontinuation and 4 of the 5 valganciclovir-treated subjects had TEAEs considered by investigators as related to study drug. The most common TEAEs in the overall maribavir group considered by investigators as related to study drug were nausea (three subjects, two in the 1,200 mg BID group and one in the 800 mg BID group) and vomiting (three subjects, two in the 1,200 mg BID group and one in the 400 mg BID group) followed by diarrhea and decreased appetite (two subjects each). All other TEAEs causing discontinuation of maribavir and considered related to study drug were reported by one subject each. In the valganciclovir group, the only TEAE causing discontinuation of study drug and considered by investigators as related to study drug reported by two subjects was leukopenia.

7.6.3.5. Dose Adjustment for Toxicity Management, Trial 203

In order to manage treatment toxicities, the study protocol allowed for dose adjustment in study drug. The proportion of subjects who had dose adjustment during the study was much higher in the valganciclovir group (48%, 19 subjects) compared to the combined maribavir group (8%, 10 subjects: 2 in the 400 mg BID group, 2 in the 800 mg BID group, and 6 in the 1,200 mg BID group). The most common reason for dose adjustment in the maribavir group was gastrointestinal toxicity (5 of the 10, 50%). For the valganciclovir group the most common reason was impairment of renal function (13/19, 68%).

7.6.3.6. Treatment-Emergent Adverse Events, Trial 203

A total of 119 subjects received at least on dose of study drug (ITT-S population). Across treatment groups, the proportion of subjects who experienced at least 1 TEAE was 98%, 95%, 100%, and 83% in the maribavir 400 mg BID, 800 mg BID, 1,200 mg BID, and valganciclovir treatment groups, respectively. The higher proportion of subjects with at least on TEAE in the maribavir groups compared to the valganciclovir group is probably due to dysgeusia, a known adverse event associated with the use of this drug.

Dysgeusia was the most common TEAE in the maribavir-treated subjects. It was reported in 40% of the overall maribavir group, with no evidence of dose dependence across the three treatment groups. On the other hand, only one subject (3%) experienced dysgeusia during treatment with valganciclovir. With regard to the three maribavir, groups, there was somewhat higher proportion of subjects with vomiting with higher maribavir doses (10% in the 400 mg BID, 20% in the 800 mg BID, and 31% in the 1,200 mg BID groups). Otherwise, there was no dose dependence among the three maribavir treatment groups for the proportion of TEAEs.

Other notable differences between the overall maribavir-treated subjects and valganciclovir were the higher proportion of maribavir-treated subjects with diarrhea (20% versus 10%), vomiting (20% versus 10%), nausea (23% versus 15%), decreased appetite (12% versus 3%), headache

(12% versus 3%), immunosuppressant drug levels increased (8% versus 0%), and renal failure (8% versus 0%).

TEAEs that occurred with similar frequency between the overall maribavir-treated subjects and valganciclovir-treated subjects included cough (14% versus 13%, urinary tract infection (13% versus 10%), abdominal pain, rash, and tremor. Peripheral edema was the most common TEAE in the valganciclovir group (18%). However, a similar frequency (14% was reported in the overall maribavir group (14%). Table 56 summarizes all TEAEs **reported in Trial 203 with frequency by at least 10% of subjects in any treatment group.**

Table 56. TEAEs Reported by at Least 10% of Subjects in Any Treatment Group (Safety Population)

Preferred Term	Maribavir 400 mg BID N=40 n (%)	Maribavir 800 mg BID N=40 n (%)	Maribavir 1,200 mg BID N=39 n (%)	Maribavir All Doses N=119 n (%)	Valganciclovir 900 mg BID N=40 n (%)
Patients with any TEAE	39 (98)	38 (95)	39 (100)	116 (98)	33 (83)
Dysgeusia	18 (45)	16 (40)	14 (36)	48 (40)	1 (3)
Nausea	9 (23)	7 (18)	11 (28)	27 (23)	6 (15)
Diarrhea	7 (18)	7 (18)	10 (26)	24 (20)	4 (10)
Vomiting	4 (10)	8 (20)	12 (31)	24 (20)	4 (10)
Cough	5 (13)	6 (15)	6 (15)	17 (14)	5 (13)
Edema peripheral	3 (8)	9 (23)	5 (13)	17 (14)	7 (18)
Urinary tract infection	5 (13)	5 (13)	6 (15)	16 (13)	4 (10)
Decreased appetite	4 (10)	5 (13)	5 (13)	14 (12)	1 (3)
Headache	4 (10)	4 (10)	6 (15)	14 (12)	1 (3)
Anemia	2 (5)	7 (18)	3 (8)	12 (10)	1 (3)
Dyspnea	3 (8)	3 (8)	6 (15)	12 (10)	2 (5)
Nasopharyngitis	7 (18)	5 (13)	0	12 (10)	2 (5)
Pyrexia	4 (10)	3 (8)	4 (10)	11 (9)	0
Weight decreased	6 (15)	2 (5)	3 (8)	11 (9)	3 (8)
Immunosuppressant drug level increased	2 (5)	2 (5)	6 (15)	10 (8)	0
Abdominal pain	2 (5)	3 (8)	4 (10)	9 (8)	3 (8)
Constipation	2 (5)	3 (8)	4 (10)	9 (8)	2 (5)
Cytomegalovirus infection	5 (13)	3 (8)	1 (3)	9 (8)	2 (5)
Renal failure	3 (8)	1 (3)	5 (13)	9 (8)	0
Hypokalemia	2 (5)	1 (3)	5 (13)	8 (7)	2 (5)
Abdominal pain upper	4 (10)	2 (5)	1 (3)	7 (6)	1 (3)
Rash	2 (5)	4 (10)	1 (3)	7 (6)	3 (8)
Tremor	1 (3)	1 (3)	4 (10)	6 (5)	1 (3)
Malaise	0	0	4 (10)	4 (3)	0

Source: adae.xpt; Software R.
Abbreviations: BID, twice daily; N, number of patients in treatment arm; n, number of patients with adverse event; TEAE, treatment-emergent adverse event

7.6.3.7. Laboratory Findings, Trial 203

Hematologic abnormalities are the major concerns with the use of valganciclovir or ganciclovir and many times lead to dose adjustment or to discontinuation of the drug. Hematologic abnormalities are also common laboratory abnormalities in transplant recipients due to the immunosuppressive medications taken by these patients. To investigate the effects of

valganciclovir on these selected laboratory abnormalities of interest and possible differences with the use of maribavir we summarize these laboratory parameters in Table 57 and Table 58.

Table 57. Selected Laboratory Abnormalities, Worse Case Reported During Treatment Period, Trial 203

Laboratory Test	Maribavir 400 mg BID N=40 n (%)	Maribavir 800 mg BID N=40 n (%)	Maribavir 1200 mg BID N=39 n (%)	Maribavir All Doses N=119 n (%)	Valganciclovir N=40 n (%)
Neutrophils (cells/µL)					
< 500	0	1 (3)	1 (3)	2 (2)	2 (5)
500 to 750	1 (3)	1 (3)	1 (3)	3 (3)	1 (3)
750 to 1000	1 (3)	1 (3)	1 (3)	3 (3)	4 (10)
Platelets (cells/µL)					
<25000	0	0	3 (8)	3 (3)	5 (13)
25000 to 50000	4 (10)	8 (20)	3 (8)	15 (13)	4 (10)
50000 to 100000	5 (13)	3 (8)	5 (13)	13 (11)	8 (20)
Hemoglobin (g/dL)					
< 6.5	1 (3)	0	0	1 (1)	0
6.5 to 8.0	4 (10)	10 (25)	8 (21)	22 (18)	2 (5)
8.0 to 9.5	12 (30)	16 (40)	14 (36)	42 (35)	11 (28)
Creatinine (mg/dL)					
> 2.5	4 (10)	2 (5)	5 (13)	11 (9)	2 (5)
1.5 to 2.5	10 (25)	16 (40)	12 (31)	38 (32)	10 (25)

Source: ad b.xpt; software, R.
Duration is 12 weeks.
Abbreviations: BID, twice daily; IAT, investigator-assigned treatment; N, number of subjects with relevant laboratory data; n, number of subjects with abnormality

Table 58. Shifts of 3 or 4 Grades From Baseline for Selected Laboratory Abnormalities, Trial 203

Laboratory Test	Maribavir 400 mg BID N=40 n (%)	Maribavir 800 mg BID N=40 n (%)	Maribavir 1,200 mg BID N=40 n (%)	Maribavir All Doses N=119 n (%)	Valganciclovir N=40 n (%)
Neutrophils decreased					
Three-grade shift	1 (3)	1 (3)	1 (3)	3 (3)	2 (5)
Four-grade shift	0	0	1(3)	1 (1)	1 (3)
Hemoglobin decreased					
Three-grade shift	0	0	1 (3)	1 (1)	0
Four-grade shift	0	0	0	0	0
Platelets decreased					
Three-grade shift	0	1 (3)	1(3)	2 (2)	2 (5)
Four-grade shift	0	0	1 (3)	1 (1)	0
Creatinine increased					
Three-grade shift	0	0	0	0	0
Four-grade shift	0	0	0	0	0

Source: ad b.xpt; Software.
Abbreviation: BID, twice daily; N, number of subjects with relevant laboratory data; n, number of subjects with indicated shift

There were no significant differences in these selected laboratory abnormalities among the three maribavir dose groups. The differences between the combined maribavir doses and valganciclovir were also not impressive. The most profound difference was in platelet counts less than 25,000 cells/ µL, neutrophils between 750 to 1000 cells/ µL, and hemoglobin levels

between 6.5 to 8.0 g/dL. Five (13%) subjects in the valganciclovir group had platelets less than 25,000 cells/µL and only 3 (3%) subjects in the combined maribavir group had platelets below that level. However, there were no differences between the combined maribavir group and valganciclovir for platelets between 25,000 and 50,000 cells/µL For platelet levels between 50,000 and 100,000 cells/ µL more subjects in the valganciclovir group compared to the combined maribavir group experienced these abnormalities (20% vs. 11%, respectively). For neutrophils between 750 to 1,000 cells/µL there were more subjects in the valganciclovir group (10%, 4 subjects) compared to the combined maribavir group (3%, 3 subjects). However, there were no differences between the two groups for the most severe forms of neutropenia (less than 500 cells/µL and between 500 to 750 cells/µL). There was only one report with hemoglobin <6.5 g/dL in the maribavir 1200 mg BID group. For hemoglobin levels between 6.5 and 8.0 g/dL there were also more reports in the combined maribavir group (18%) compared to the valganciclovir group (5%). Slightly higher reports in increased creatinine levels occurred in the combined maribavir group compared to the valganciclovir group.

To further explore potential differences in laboratory abnormalities between the maribavir and valganciclovir, we compared the shifts of 3 or 4 grades in the previously described laboratory abnormalities. No significant differences were noted between the treatment groups. Overall, the differences between the combined maribavir group and the valganciclovir group were minimal and not to the expected degree with the use of valganciclovir. These results could be due to the close monitoring of the study subjects and the dose adjustment when signs of toxicity were observed. As previously stated, the proportion of subjects who had dose adjustment during the study was much higher in the valganciclovir group compared to the combined maribavir group (48% vs. 8%, respectively).

7.7. Key Review Issues Relevant to Evaluation of Risk

7.7.1. Treatment-Emergent Resistance to Maribavir

Issue

Maribavir has a low genetic barrier to resistance.

Background

Resistance to maribavir can occur as a result of amino acid substitutions in pUL97 and pUL27. In pUL97, amino acid substitutions L337M, F342S/Y, V353A, K355del, V356G, L397R, T409M, H411L/N/Y, D456N, V466G, C480F/R, P521L, and Y617del have been reported to confer reduced susceptibility to maribavir (Chou et al. 2007a; Chou and Marousek 2008; Chou et al. 2012; Chou et al. 2013; Chou et al. 2019). The increases in EC_{50} value associated with these substitutions ranged from 3.4- to >200-fold. Furthermore, HCMV carrying substitutions that confer reduced susceptibility to maribavir do not affect the growth of recombinant HCMV in cell culture, indicating that these pUL97 substitutions do not significantly impact the fitness of virus. With respect to pUL27 and maribavir resistance, amino acid substitutions E22stop, W153R, L193F, C218del, R233S, A269T, 301 to 311del, L335P, V353E, W362R, W362stop, L426F, and

the combination of A406V and C415stop have been reported to reduce susceptibility to maribavir (Komazin et al. 2003a; Chou et al. 2004; Chou 2009; Chou et al. 2012). The increases in EC_{50} value for these substitutions ranged from 1.7-fold to 23-fold. HCMV carrying pUL27 substitutions that reduce susceptibility to maribavir do not affect the growth of recombinant HCMV in cell culture, indicating that these substitutions do not significantly impact the fitness of virus. Resistant virus with amino acid substitutions in both pUL27 and pUL97 has also been reported (Chou et al. 2007b).

Assessment

In the original NDA submission, 118 total paired baseline and failure pUL27 and pUL97 sequences (n=80 and 38 in the maribavir and IAT arms, respectively) for the treatment-emergent resistance analysis from study 303 were submitted. The Applicant subsequently submitted additional paired sequences in SDN 003. Thus, 196 paired sequences (134 and 62 in the maribavir and IAT arms, respectively) were available for the treatment-emergent resistance analysis. The majority of the virologic failures were on-treatment failures.

In the virologic failures from the maribavir treated arm in study 303, maribavir resistance-associated pUL97 amino acid substitutions identified in cell culture selection experiments as well as in the Applicant's Phase 2 studies 202 and 203 were frequently observed using Sanger nucleotide sequence analysis: F342Y (n=3; 4.5-fold reduction in susceptibility to maribavir), T409M (n=29; 81-fold reduction), H411L (n=1; 69-fold reduction), H411N (n=2; 9-fold reduction), H411Y (n=23; 12-fold reduction), and C480F (n=20; 224-fold reduction) (Table 59, FDA analysis). T409M and H411L/N/Y are maribavir specific resistance-associated substitutions. F342 (6-fold reduction to valganciclovir/ganciclovir) and C480 (2.3-fold reduction to valganciclovir/ganciclovir) may have been enriched by valganciclovir/ganciclovir to levels below the detection of the Sanger nucleotide sequence assay and therefore their association with maribavir resistance is unclear. Of note, one subject only developed the pUL97 F342Y substitution (4.5-fold reduction to maribavir in cell culture) which provides a maximum floor for the reduction in susceptibility that could predict failure. Additionally, known valganciclovir/ganciclovir resistance-associated substitutions emerged upon treatment with maribavir at pUL97: K359E (n=1), H520Q (n=2), A594V (n=1), L595F (n=1), L595S (n=1), E596G (n=1), and C603W (n=1). All 8 of these subjects were previously treated with valganciclovir/ganciclovir prior to being treated with maribavir. While these valganciclovir/ganciclovir resistance-associated substitutions may have been present at low levels prior to maribavir treatment, the Applicant should evaluate the susceptibility of maribavir in cell culture for any substitutions that have not previously been evaluated. This assessment is especially important for pUL97 K359E given that several maribavir resistance-associated substitutions are near this pUL97 amino acid (pUL97 V353A, K355del, and V356G). The other treatment-emergent pUL97 substitutions that were observed in more than one virologic failure are pUL97 N68D (n=6), L126Q (n=6), P132L (n=2), and I244V (n=6). However, all of these are at polymorphic positions. Several subjects had these substitutions at baseline and their response rates were similar to that of the overall response rate (see baseline polymorphism analyses above). Substitutions pUL97 N68D, L126Q, and I244V are common polymorphisms identified in the HCMV Towne strain and other clinical isolates that were phenotyped as maribavir-susceptible. Additionally, none of these substitutions are close to positions that have previously been identified as maribavir resistance-associated. Therefore, these substitutions are not likely to be associated with resistance to maribavir. However, pUL97 P132L is not present in the HCMV Towne strain or in any of the clinical

isolates that have previously been assessed for maribavir susceptibility. Therefore, this substitution should be phenotyped as polymorphic positions can be associated with resistance. Of note, no new amino acid substitutions at previously identified maribavir resistance-associated positions were seen. Substitution pUL97 P132L is at a novel position. In the IAT arm, known valganciclovir/ganciclovir resistance-associated pUL97 amino acid substitutions were observed at K359E (n=1), H520Q (n=1), A594V (n=1), and L595S (n=1).

Importantly, several pUL97 maribavir resistant-associated substitutions developed at positions T409 (T409M=29) and H411 (H411L=1, H411N=2, H411Y=23). These are maribavir specific resistance-associated substitutions while those at F342 and C480 may have been selected by valganciclovir/ganciclovir but were below the detection of the assay at baseline. These data further support the antiviral activity of maribavir.

Table 59. Treatment-Emergent Amino Acid Substitutions in pUL97

pUL97 Substitution	MBV (N=134)	IAT (N=62)	% Identity	Most Common Amino Acid(s) Reported at This Position[#]
T17P	1	0	100	T
Q19E	4	1	84.5	Q, E, R
D66G	0	1	100	D
N68D	6	2	7.9	N, D
A78T	1	0	100	A
G79C	1	0	100	G
T87S	1	0	100	T
F102L	1	0	100	F
R112C	1	0	96	R, C, H
L126Q	4	1	49.5	L, Q
R127C	1	0	100	R
P132L	2	0	94.1	P, A, L, S

pUL97 Substitution	MBV (N=134)	IAT (N=62)	% Identity	Most Common Amino Acid(s) Reported at This Position[#]
S133F	1	0	99.3	S, P
S136F	1	0	100	S
R173H	0	1	100	R
S187G	1	0	98.7	S, G
S235G	1	0	99.7	S, N
I244V	3	0	8.6	I, V
P247S	1	0	97.4	P, S
F342Y*	**3**	**0**	**100**	**F**
K359E	***1***	***0***	***100***	***K***
Q382del	0	1	100	Q
Q383del	0	1	100	Q
T409M	**24**	**0**	**100**	**T**
H411L	**1**	**0**	**100**	**H**
H411N	**2**	**0**	**100**	**H**
H411Y	**14**	**0**	**100**	**H**
H420N	1	0	100	H
A427T	1	0	99.3	A, T
C453F	0	1	100	C
N470S	0	1	100	N
C480F*	**13**	**0**	**100**	**C**
R516H	0	1	100	R
H520Q	***0***	***1***	***100***	***H***
L553S	1	0	100	L
G557D	1	0	100	G
G561S	1	0	100	G
R570Q	1	1	100	R
F585L	1	0	100	F
A594V	*1*	*1*	*100*	*A*
L595F	***1***	***1***	***100***	***L***
L595S	***1***	***1***	***100***	***L***
E596G	1	0	100	E
C603W	***1***	***0***	***100***	***C***
D605E	1	1	96	D, E
L608P	1	0	100	L
S616G	1	0	100	S
E624K	1	0	100	E
D677V	0	1	100	D
Total substitutions	134	22		

Source: FDA analysis.
Bold: Previously identified maribavir resistance-associated substitutions.
Bold italics: Previously identified valganciclovir/ganciclovir resistance-associated substitutions.
* Cross-resistant to valganciclovir/ganciclovir.
[#] Ordered based on decreasing frequency.
Abbreviations: IAT, investigator-assigned treatment; MBV, maribavir; N, number of subjects in study arm

In the maribavir treatment arm, no treatment-emergent pUL27 resistance-associated substitutions previously reported to confer resistance to maribavir were found using Sanger sequence analysis (Table 60, FDA analysis). Treatment-emergent pUL27 substitutions P10L (n=2), L11P (n=2), H97R (n=2), L133I (n=2), N289D (n=5), H297Y (n=2), D298G (n=6), N300G (n=5), P307L

(n=4), V310A (n=5), D351N (n=5), I367V (n=6), H557Q (n=2), and A565T (n=2) were observed in 2 or more virologic failures. All of these substitutions are at previously known polymorphic positions found in lab strains and clinical isolates without prior maribavir exposure. Most of these substitutions were present at baseline and the response rates in subjects with these substitutions were similar to that of the overall response rate (see baseline polymorphism analyses above). Furthermore, substitutions pUL27 L11P, H97R, L133I, H557Q, and A565T are not close to positions that have previously been identified as maribavir resistance-associated. Therefore, these substitutions do not need to be characterized at this time. However, if they are observed as treatment-emergent in virologic failures from the ongoing study 302, they may need to be characterized. Substitutions pUL27 H297Y, D298G, N300G, P307L, V310A, D351N, and I367V emerged in positions that are close to positions that have previously been identified as maribavir resistance-associated (del D301-A311, V353E, and W362R (Chou 2009).

Additionally, pUL27 P10L (n=1 of 2 total occurrences), N289D (n=4 of 5 total occurrences), D298G (n=4 of 6 total occurrences), N300G (n=4 of 5 total occurrences), P307L (n=3 of 4 total occurrences), V310A (n=3 of 5 total occurrences), and I367V (n=4 of 6 total occurrences) were found with pUL97 resistance-associated substitutions T409M (confers an 81-fold reduction in susceptibility), H411N (confers a 9-fold reduction), H411Y (confers a 12-fold reduction), and/or C480F (confers a 224-fold reduction) so they need to be characterized. Of note, the pUL27 H297Y substitution is of particular interest as the response rate in subjects who had a pUL27 H297Y substitution at baseline was 40% (16 of 40) compared to 55.74% (131 of 235) for the total response rate. A disproportionate number of treatment-emergent pUL27 substitutions was found in the maribavir arm (n=76) compared to the IAT arm (n=18), and these substitutions were concentrated in a smaller subset of the virologic failures (12 subjects and 3 subjects in the maribavir arm and IAT arm, respectively). Furthermore, three of these subjects also had the previously unidentified pUL97 L126Q substitution described above. Substitutions pUL27 P10L, N289D, H297Y, D298G, N300G, P307L, V310A, D351N, and I367V should be phenotyped. It is possible that high level resistance to maribavir might be due to resistance-associated substitutions occurring in two different proteins within the virus, similar to valganciclovir/ ganciclovir. While the disproportionate number of emergent substitutions are concerning. as some of these may be resistance-associated, the data are inconclusive given that the majority of the virologic failures (n=111 subjects) did not have any treatment-emergent pUL27 substitutions. As stated above, the Applicant will need to phenotype pUL27 P10L, N289D, H297Y, D298G, N300G, P307L, V310A, D351N, and I367V.

Table 60. Treatment-Emergent Amino Acid Substitutions in pUL27

pUL27 Substitution	MBV (N=134)	IAT (N=62)	% Identity	Most Common Amino Acid(s) Reported at This Position[a]
P10L	1	0	97.3	P, L, S
L11P	2	2	66.3	L, P
P12L	1	0	84.1	P, L, S
P12S	1	0	84.1	P, L, S
E22D	1	0	99.6	E, D
E22del	1	0	99.6	E, D
E49G	0	1	100	E
T61M	1	0	100	T
A84P	1	0	94.7	A, P, V
A84V	0	1	94.7	A, P, V
K90R	1	1	84.8	K, R
H97R	2	0	97	H, R
L133I	2	0	95.8	L, I
A134T	1	0	99.6	A, T
Q167R	0	1	100	Q
R246H	1	0	98.9	R, H
D288E	1	0	99.6	D, N
N289D	5	0	20.8	N, D
H293R	1	0	99.6	H, R
D294G	1	0	74.2	D, G, N
D294N	1	1	74.2	D, G, N
D294S	1	0	74.2	D, G, N
N296G	1	0	99.2	N, S
H297Y	2	1	79.5	H, Y
D298G	6	0	9.8	D, G
G299del	1	0	99.6	G, S
N300D	1	1	24.2	N, G
N300G	5	2	24.2	N, G
N300S	1	1	24.2	N, G
D301N	1	0	96.2	G, S
P307L	4	1	44.7	P, L, S
V310A	5	2	43.9	V, A
A347T	1	0	100	A
D351N	5	1	39	D, N
I367V	6	0	12.9	I, V
R465C	1	0	90.9	R, C
T519A	1	0	97.7	T, A
A520V	1	0	97.7	A, V
R531Q	1	0	99.2	R, Q
A535V	1	0	100	A
H557Q	2	0	77.3	H, Q
A558V	1	0	90.9	A, V
A565T	2	0	83.7	A, T
Total substitutions	76	18		

Source: FDA analysis.
[a] Ordered based on decreasing frequency.
Abbreviations: IAT, investigator-assigned treatment; MBV, maribavir; N, number of subjects in study arm

In the maribavir treatment arm, S290R (n=2), K475R (n=3), S655L (n=5), N685S (n=5), A885T (n=5), S897L (n=5), N898D (n=4), and A1122T (n=6) were observed using Sanger sequence analysis in at least two virologic failures (note: none of these are known valganciclovir/ ganciclovir resistance-associated substitutions) (Table 61, FDA analysis). Amongst the ones at polymorphic positions (S655L, N685S, A885T, S897L, N898D, A1122T), several subjects had these substitutions at baseline and the response rates for each were similar to that of the overall response rate (see baseline polymorphism analyses above). Of note, a disproportionate number of treatment-emergent substitutions in the maribavir arm (n=76) was found compared to the IAT arm (n=35), although not to the extent as was observed in the pUL97 and pUL27. Similar to those in pUL27 these substitutions were concentrated in a smaller subset of the virologic failures (27 subjects and 10 subjects in the maribavir arm and IAT arm, respectively). Of note, a larger disproportion of treatment-emergent pUL54 substitutions was found based on the review of the data submitted with the original NDA submission. According to the Applicant's response in SDN 014, the data originally submitted were based on an interim dataset. Additional pUL54 genotyping was completed from available samples from virologic failures and the difference between the arms narrowed. Given the Applicant's biochemical data demonstrating a lack of activity against HCMV DNA polymerase and human polymerase delta, the small difference between the arms is not considered due to selection by maribavir.

All nine subjects in the maribavir arm who had treatment-emergent valganciclovir/ganciclovir pUL54 resistance-associated substitution(s) had previous valganciclovir/ganciclovir exposure. Since maribavir has been demonstrated to have no activity against HCMV DNA polymerase in preliminary biochemical studies (see nonclinical virology section above), most of these substitutions were at polymorphic positions, and no pUL54 resistance-associated substitutions have been selected by maribavir to-date in cell culture studies, they are less likely to be associated with maribavir resistance. However, there appears to be more treatment-emergent substitutions in the maribavir arm. As the phenotypic assays are time consuming, the Applicant should prioritize the substitutions that were identified in the pUL97 and pUL27, as described above. However, the Applicant should subsequently phenotypically characterize the pUL54 substitutions at highly conserved positions and that emerged in at least 2 virologic failures (pUL54 S290R and K475R). These results are consistent with the Applicant's biochemical studies where the 5'-mono- and 5'-triphosphate derivatives of maribavir at 100μM against HCMV DNA polymerase and human polymerase delta had no significant effect on the incorporation of deoxynucleoside triphosphates. However, pending the results of pUL54 S290R and K475R, the Applicant may also need to characterize the known valganciclovir/ganciclovir resistance-associated substitutions that emerged.

Table 61. Treatment-Emergent Amino Acid Substitutions in pUL54

pUL54 Substitution	IAT (N=62)	MBV (N=134)	% Identity	Most Common Amino Acid(s) Reported at This Position[a]
M1Y	0	1	100	M
F2V	0	1	100	F
T12A	0	1	98.9	T, A
A15V	0	1	98.6	A, T, V
P116S	0	1	99.3	P, L, S
T164I	1	0	100	T
S290R	0	2	100	S
T369I	1	0	100	T
N408D	**0**	**1**	**100**	**N**
F412V	**1**	**0**	**100**	**F**
E422Q	0	1	100	E
K475G	0	1	100	K
K475R	0	3	100	K
V476L	0	1	100	V
T503I	**0**	**1**	**100**	**T**
K513N	**0**	**1**	**100**	**K**
L516P	**1**	**1**	**100**	**L**
L545S	**1**	**0**	**100**	**L**
Q578H	**2**	**0**	**100**	**Q**
C590F	1	1	100	C
V627M	1	0	100	V
G629S	0	1	98.6	G, S
F638C	0	1	100	F
F638G	0	1	100	F
F638V	0	1	100	F
Q639R	2	0	100	Q
M640W	1	0	99.3	M, R
S655L	1	5	40.9	S, L
S676G	0	1	97.9	S, G
S676R	1	0	97.9	S, G
N685S	1	5	32	N, S, insT
G687S	0	1	99.6	G, S
V715M	**0**	**1**	**100**	**V**
G740D	1	0	100	G
E756K	1	0	100	E
L773V	**1**	**1**	**100**	**L**
L776M	**1**	**0**	**100**	**L**
A809V	1	0	100	A
A834P	**1**	**0**	**100**	**A**
G841A	**1**	**1**	**100**	**G**
G841S	**0**	**1**	**100**	**G**
A849E	0	1	100	A
K853V	0	1	100	K
G874R	0	1	91.8	G, R
D879N	0	1	100	D
E882insS	1	0	100	E
A885T	4	5	96.1	A, T
E888K	1	0	100	E
G889R	0	1	100	G
L890F	0	1	93.2	L, F
S894L	0	1	100	S

pUL54 Substitution	IAT (N=62)	MBV (N=134)	% Identity	Most Common Amino Acid(s) Reported at This Position[a]
S897L	2	5	73.3	S, L
N898D	1	4	21	N, D
A987G	**0**	**1**	**100**	**A**
G1105D	0	1	99.3	G, D
N1116H	0	1	92.2	N, H
A1122P	0	1	39.5	A, T, V
A1122T	2	6	39.5	A, T, V
D1132Y	0	1	100	D
G1142R	0	1	100	G
S1146G	0	1	97.5	S, G, N
N1147S	0	1	94	N, S
A1154P	2	0	98.9	A, P, T
G1207D	0	1	98.9	G, D
M1219V	0	1	100	M
S1235T	0	1	97.9	S, T
Total substitutions	35	76		

Source: FDA analysis.
Bold: valganciclovir/ganciclovir and/or cidofovir and/or foscarnet resistance-associated substitutions.
[a] Ordered based on decreasing frequency.
Abbreviations: IAT, investigator-assigned treatment; MBV, maribavir; N, number of subjects in study arm

As stated above, 196 paired sequences (134 and 62 in the maribavir and IAT arms, respectively) were available for the treatment-emergent resistance analysis. Amongst the 134 paired sequences in the maribavir arm, 58 had one or more of the treatment-emergent pUL97 maribavir resistance-associated substitutions. Amongst the 58, 19 subjects had two or more maribavir resistance-associated substitutions in pUL97 (pUL97 F342Y+H411Y [n =1], pUL97 F342Y+T409M+H411N [n =1], pUL97 H411Y+C480F [n =2], pUL97 H411L+C480F [n =1], pUL97 T409M+C480F [n =6], and pUL97 T409M+H411Y [n =8]). Additionally, 6 (amongst the 58) also had one or more treatment-emergent pUL27 substitutions (pUL27 E22D, H97R, N289D/G, N300G, P307L, V310A, I367A). Of note, 47 of these were observed in subjects who had on-treatment failure, while only 11 were from subjects who experienced a relapse (Table 62, FDA analysis). Importantly, 62% (47 of 76) of the subjects who were on-treatment failures had a treatment-emergent maribavir resistance-associated substitution in pUL97. In contrast, only 23% (11 of 48) of the subjects who experienced a relapse had a treatment-emergent maribavir resistance-associated substitution (note: ten subjects who were slow responders, i.e., achieved <LLOQ at Week 8 and did not experience a subsequent relapse were excluded from these calculations). The relatively lower rate of detection of the maribavir resistance-associated substitution(s) in the subjects who experienced a relapse indicates that these subjects may have benefited from longer treatment, consistent with the viral decay analyses. Of note, the persistence of the maribavir resistance-associated substitutions is difficult to address as these virologic failures often need to be treated by alternative therapy immediately. However, based on the cell culture studies, viruses with these substitutions do not impact the fitness. Consistent with the nonclinical findings, two subjects who experienced virologic breakthrough retained their maribavir resistance-associated substitutions in their Week 20 samples. Of note, HCMV resistant virus probably becomes latent based on foscarnet studies (Rodriguez et al. 2007).

Table 62. Individual Subjects Who Developed Maribavir Resistance by Timepoint

Subject ID (b) (6)	Met Primary Endpoint at Wk 8	Recurrence in 12-Wk FU	Reason For Failure	Isolate	pUL97 F342	pUL97 T409	pUL97 H411	pUL97 C480	MBV Fold Shift of Substitution in Cell Culture
303	No		Breakthrough	Wk 8		M			81
303	No		Non-responder	Wk 8		M			81
303	No	No	Breakthrough	Wk 8			Y		12
303	No		Rebound	Wk 8		M/T		C/F	N/A
303	No	No	Breakthrough	Wk 7				C/F	224
	No	No	Breakthrough	Wk 8		M			81
303	No	No	Breakthrough	Wk 8				F	224
303	Yes	Yes	Relapse	Wk 11			Y/H		12
303	No	No	Breakthrough	Wk 8			Y		12
303	No	No	Breakthrough	Wk 8		M			81
303	Yes	Yes		Wk 12			Y/H		12
303	No	No	Breakthrough	Wk 10				F	224
303	No	No	Breakthrough	Wk 8		M/T	Y/H		N/A
303	No		Breakthrough	Wk 8		M			81
303	No		Rebound	Wk 6		M/T			81
	No		Rebound	Wk 8		M/T	Y/H		N/A
303	No		Non-responder	Wk 8		M/T	Y/H		N/A
303	No		Rebound	Wk 8		M/T			81
303	Yes	Yes	Relapse	Wk 18			Y/H		12
303	No		Breakthrough	Wk 8		M/T	Y/H		N/A
303	No		Rebound	Wk 8	Y	T/M	N/H		N/A
303	No	No	Breakthrough	Wk 8				F	224
	No	No	Breakthrough	Wk 9			Y		12
303	No	No	Breakthrough	Wk 8				F	224
303	No	No	Breakthrough	Wk 7		M			81
303	No	No	Breakthrough	Wk 8			H/L	C/F	N/A
303	No	No	Rebound	Wk 8			N/H		9
303	Yes	Yes	Relapse	Wk 11			Y		12
303	No	No	Breakthrough	Wk 8		T/M		C/F	N/A
303	Yes	Yes	Relapse	Wk 12			Y/H		12
303	No		Breakthrough	Wk 8		M/T	Y/H		N/A
303	No		Rebound	Wk 4	Y				4.5
	No		Rebound	Wk 7	Y		Y/H		12

Subject ID	Met Primary Endpoint at Wk 8	Recurrence in 12-Wk FU	Reason For Failure	Isolate	pUL97 F342	pUL97 T409	pUL97 H411	pUL97 C480	MBV Fold Shift of Substitution in Cell Culture
303-(b) (6)	No		Breakthrough	Wk 8			Y		12
303-	No	No	Non-responder	Wk 4	Y/F				4.5
303-	Yes	Yes	Relapse	Wk 11		M			81
303-	No	No	Breakthrough	Wk 8		M			81
303-	No		Rebound	Wk 6		T/M		C/F	N/A
303-	Yes	Yes	Relapse	Wk 11		M/T			81
303-	No	No	Breakthrough	Wk 8				F	224
303-	No		Non-responder	Wk 4		T/M			81
303-	No	No	Breakthrough	Wk 8		M			81
303-	No	No	Breakthrough	Wk 8				F	224
303-	No	No	Breakthrough	Wk 8		M			81
	No	No	Breakthrough	Wk 9			Y		12
303-	Yes	Yes	Relapse	Wk 10				C/F	224
303-	No	No	Breakthrough	Wk 8		M			81
	No	No	Breakthrough	Wk 9		T/M		C/F	N/A
303-	No	No	Breakthrough	Wk 8		M/T	Y/H		N/A
303-	No		Breakthrough	Wk 7		M			81
303-	No	Yes	Rebound	Wk 6			Y		12
303-	No	No	Breakthrough	Wk 8		M			81
303-	No		Rebound	Wk 8		T/M	Y/H		N/A
303-	Yes	Yes	Relapse	Wk 11		M/T			81
303-	No	No	Breakthrough	Wk 8				F	224
303-	No	No	Breakthrough	Wk 8				F	224
303-	No	No	Breakthrough	Wk 9				F	224
303-	No		Rebound	Wk 6			Y		12
303-	Yes	Yes	Relapse	Wk 12			Y		12
303-	No	No	Breakthrough	Wk 8			Y/H	C/F	N/A
303-	No	No	Breakthrough	Wk 8				F	224
303-	No	No	Breakthrough	Wk 6				F	224
303-	No		Rebound	Wk 6		T/M		C/F	N/A
303-	Yes	Yes	Relapse	Wk 12			Y/H		12

Source: FDA analysis.
Non-responder: Subjects whose viral load did not decline by at least 1-log.
Rebound: Subjects whose viral load declined by at least 1-log but never achieved <LLOQ, then increased by at least 1-log from nadir while on therapy.
Breakthrough: Subjects who achieved viral load <LLOQ and subsequently became detectable while on therapy.
Relapse: Subjects who achieved viral load <LLOQ through Week 8 and subsequently became detectable while off therapy.
Abbreviations: FU, follow-up; ID, identity; MBV, maribavir; N/A, not applicable; Wk, week

Of note, of the 58 subjects randomized to maribavir arm who developed maribavir resistance-associated substitutions, 48 subjects were subsequently treated with alternative HCMV antivirals. Amongst the 48 maribavir failures who were retreated with alternative HCMV treatments (i.e., ganciclovir/foscarnet/cidofovir/letermovir), 24 had baseline resistance-associated substitution (RAS) to the IAT drugs (i.e., there were 24 subjects each in the resistant and refractory categories).

Amongst the 24 subjects in the resistant category (i.e., had baseline IAT RAS), 12 (50%) were able to achieve <LLOQ after retreatment with the IAT. Amongst the 12 who did respond, all were initially treated with ganciclovir (i.e., prior to enrolling in the study/maribavir arm). The breakdown of the treatment post-maribavir failure of the 12 who did respond were 5 who received valganciclovir/ganciclovir only, 4 who received foscarnet only, 2 who received valganciclovir/ganciclovir + at least one of foscarnet/cidofovir/letermovir, and 1 who received letermovir (note: 7 of 12 received treatment that is different from what they originally failed (i.e., valganciclovir only). Amongst the 5 who received valganciclovir/ganciclovir only as the post-maribavir treatment (i.e., these are the subjects who failed ganciclovir, then failed maribavir, then got retreated with ganciclovir) and responded, one did not have a pUL97 ganciclovir RAS at baseline (i.e., a rare one that only had the UL54). The pUL54 RAS was the P522A (3-fold reduction to ganciclovir) and no additional treatment-emergent maribavir RAS, which might have conferred cross-resistant to ganciclovir, so it is not surprising that this subject responded to ganciclovir. Additionally, it is not clear if a higher dose of ganciclovir and/or change immunosuppression was used. Three subjects had a pUL97 ganciclovir RAS at baseline but did not acquire additional treatment-emergent maribavir RAS that could confer cross-resistance to ganciclovir. All three baseline ganciclovir RAS are in the low to intermediate fold-shift range so not necessarily surprising that they responded to ganciclovir. One subject had a pUL97 ganciclovir RAS at baseline and acquired an additional treatment-emergent maribavir RAS that is cross-resistant to ganciclovir and still responded.

Amongst the 24 subjects in the refractory category (i.e., no baseline IAT RAS), 18 (75%) were able to achieve <LLOQ after retreatment with the IAT. Amongst the 18 who did respond, 17 were initially treated with ganciclovir (i.e., prior to enrolling in the study/maribavir arm) and 1 was treated with foscarnet. The breakdown of the treatment post-maribavir failure of the 18 who did respond were 11 who received valganciclovir/ganciclovir only, 1 who received foscarnet only, 5 who received valganciclovir/ganciclovir + at least one of foscarnet/cidofovir/letermovir, and 1 who received foscarnet/letermovir. Amongst the 18 responders, 12 had treatment-emergent maribavir RAS that were cross-resistant to ganciclovir.

Amongst the 48 maribavir failures who were retreated with alternative HCMV treatments (ganciclovir/foscarnet/cidofovir/letermovir), there were 20 who had treatment-emergent maribavir RAS that are cross-resistant to ganciclovir. Fourteen of these were able to achieve <LLOQ after retreatment with the IAT. Amongst the 14 described above, 12 were refractory, 2 were resistant to IAT at baseline. Of the 2 who were resistant, one is described above (amongst the 5 who received valganciclovir/ganciclovir only post maribavir failure). The other subject received foscarnet. Amongst these 14 described above, 8 were re-treated with ganciclovir only. Seven of 8 were originally in the refractory group, i.e., when they failed maribavir treatment and acquired the maribavir RAS that is cross-resistant to ganciclovir, it was the subject's only RAS. All 8 had a maribavir RAS (pUL97 C480F) that is cross-resistant to ganciclovir and confers 2.3-fold reduced susceptibility to ganciclovir. Therefore, it is not surprising that all 8 responded

to ganciclovir. Nine subjects had multiple IAT RAS at the time of IAT retreatment. Only 4 of these 9 subjects achieved <LLOQ after the IAT re-treatment and only 1 was treated with ganciclovir (the same subject who is describe above). The other 3 responded to foscarnet or foscarnet+letermovir, which makes sense since none had foscarnet RAS. Additionally, of these 9, only 2 were treated with ganciclovir alone; the one subject who achieved <LLOQ described above and another subject who failed the retreatment. Of the subjects who had maribavir treatment-emergent RAS that is cross-resistant to ganciclovir with the higher fold-shift (6-fold), none were treated with ganciclovir alone. One subject with a higher fold-shift RAS responded to foscarnet treatment while the other subject did not respond to a combination of foscarnet and ganciclovir.

Overall, it is not surprising that many subjects responded to re-treatment given that most received treatment that was different from what they had originally failed and/or received a combination of drugs. While there were 8 subjects who developed maribavir RAS that is cross-resistant to ganciclovir and all responded to ganciclovir retreatment, it is premature to conclude that cross-resistance is not an issue given that a) there were only 8 subjects, b) all 8 had pUL97 C480Y (2.3-fold reduced susceptibility to ganciclovir) and 7 of 8 had only this RAS, and c) the preliminary data for the maribavir RAS pUL97 F342Y (6-fold reduced susceptibility to ganciclovir) were not promising (see above). While it is reassuring that all 8 responded to ganciclovir only re-treatment, often times, when subjects fail ganciclovir and develop a low fold-shift RAS, they are still kept on ganciclovir, though the ganciclovir dose may be increased, and many will respond. But a subset of these subjects will fail again later as they acquire additional ganciclovir RAS conferring greater reduced susceptibility. Additional data are necessary to make any formal conclusions.

Conclusion

Maribavir has a low genetic barrier to resistance as there were many subjects with treatment-emergent resistance-associated substitutions in virologic failures. However, the resistant/refractory subjects **may not have alternative treatment options, so this issue will be addressed in labeling.**

We will be requesting postmarketing requirements for **further characterization of the following substitutions:**

- High priority, pUL97:
  - M460I/T
  - A594E/P/T/V
  - L595F/W
  - C603R/W/Y
- Medium priority, pUL97:
  - A440V
  - V466M
  - A591V
  - E596G
  - K599E
  - C607F/Y

Rationale: Known valganciclovir/ganciclovir resistance-associated substitutions for which maribavir susceptibility has not been evaluated. These substitutions have previously been characterized and the constructs/strains should be available (Lurain and Chou 2010; Chou et al. 2020).

- Low priority:
  - pUL97
    - P132L
    - L405P
    - C518Y
    - I610T
    - A613V
  - pUL27
    - P10L
    - N289D
    - H297Y
    - D298G
    - N300G
    - P307L
    - V310A
    - D351N
    - I367V
  - pUL54
    - S290R
    - K475R

Rationale: Multiple occurrences in virologic failures.

The Applicant will need to generate recombinant virus with amino acid substitutions in order to phenotypically characterize them **in cell culture studies.**

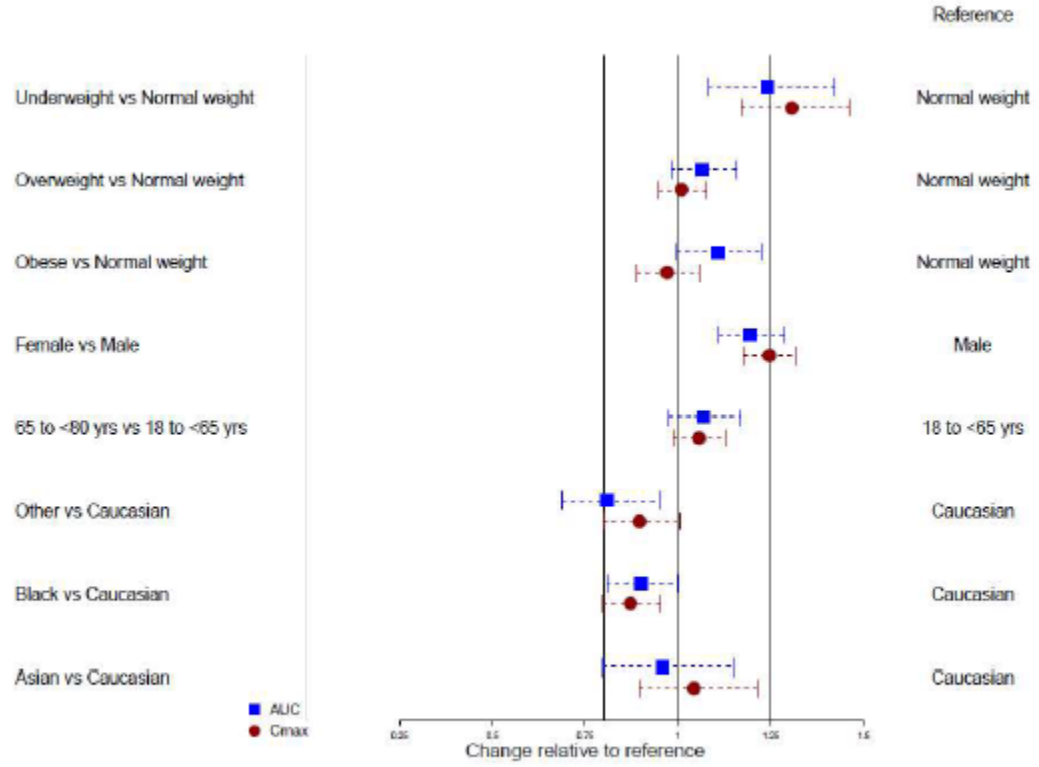
8. Therapeutic Individualization

8.1. Intrinsic Factors

8.1.1. Body Weight, Gender, Age, Race, Ethnicity

The population PK model contained PK data from 667 subjects in 12 studies of healthy volunteers and transplant patients Age ranged from 18 to 79 years and body mass index ranged from 15 to 50 kg/m^2. Age, gender, race, ethnicity, and body weight were not found to have a significant effect on the PK of maribavir (Figure 4). Refer to Section III.14.4.1 for details.

Figure 4. PopPK Analysis for the Effect of Intrinsic Factors on the PK of Maribavir



Under-weight=BMI<18.5 kg/m^2, normal weight=18.5≤BMI<25 kg/m^2, over-weight =25≤BMI<30 kg/m^2, obese=BMI≥30 kg/m^2
Source: 171sim.tab
Source: PK modeling report.
Abbreviations: AUC, area under the concentration-time curve; BMI, body mass index; C_{max}, maximum concentration; PopPK, population pharmacokinetics; PK, pharmacokinetics

8.1.2. Renal Impairment

Renal impairment study 1263-101 enrolled subjects with mild to moderate (creatinine clearance 30 to 80 mL/min) and severe (<30 mL/min) renal impairment and those with normal renal function (>80 mL/min) (Section III.14.2). Mean unbound fraction (2% in healthy subjects) was 1.1%, 1.2%, and 1.5% in subjects with mild, moderate, or severe renal impairment. Geometric mean total and unbound maribavir C_{max} and AUC ratios (renal impairment/normal renal function) ranged from 0.96 to 1.23. Labeling states that there are no clinically significant differences in the PK of maribavir based on mild to severe renal impairment.

8.1.3. Hepatic Impairment

Hepatic impairment study 1263-103 enrolled subjects with moderate hepatic impairment and those with normal hepatic function (Section III.14.2). Mean unbound fraction was 1.5% in healthy controls and 1.3% in subjects with moderate hepatic impairment. Geometric mean total and unbound maribavir C_{max} and AUC ratios (moderate hepatic impairment/normal hepatic function) ranged from 1.03 to 1.35. Labeling states that there are no clinically significant differences in the PK of maribavir based on mild or moderate hepatic impairment. Compared to the ~2-fold increase in C_{max} and AUC between the median and 95th percentile in Phase 3 study

303, the up to 35% increase in exposure in the renal and hepatic impairment studies is not significant.

8.2. Drug Interactions

8.2.1. Effects of Other Drugs on Maribavir

Maribavir is primarily eliminated by CYP3A4 (major) and CYP1A2 (minor)-mediated hepatic metabolism. Maribavir is a substrate of uridine 5'-diphospho-glucuronosyltransferases 1A1, 1A3, and 2B7, but the contribution of glucuronidation to metabolism is considered low. Maribavir is a substrate of P-glycoprotein (P-gp), BCRP, and OCT1 (Table 63).

Clinical drug-drug interaction (DDI) studies were conducted with ketoconazole (strong CYP3A and P-gp inhibitor), rifampin (strong CYP3A inducer), and an antacid (Figure 5). Clinical index inhibitors of BCRP or OCT1 are not available for DDI studies. Also, BCRP-mediated interactions typically result in a <2-fold exposure increase of the substrate, while for maribavir there are safety data for exposures three-fold higher than observed at the recommended dose.

The ~50% maribavir AUC increase when coadministered with ketoconazole is not clinically significant. This is based on absence of safety issues (per the Clinical reviewer) in Phase 2 studies at a maribavir dose of up to 1,200 mg BID, which is three times the recommended dose/exposure. In addition, at a dose of 400 mg BID in Phase 3 study 303, an ~2-fold increase in C_{max} or AUC is the difference between the median and ~95th percentile (Table 64).

Based on the ~80% maribavir C_{trough} reduction when coadministered with strong CYP3A inducer rifampin, coadministration with rifampin is not recommended. Coadministration with moderate CYP3A inducer rifabutin could potentially result in a >50% maribavir exposure reduction; due to a potential reduction in efficacy, use of maribavir with rifabutin is not recommended. Of note, in Phase 3 study 303, response rate was slightly lower at higher AUC and C_{trough} values and going from the median to 5th percentile of C_{trough} is a difference of ~80% (Table 64).

Coadministration with an antacid resulted in 11% lower maribavir AUC, which is not clinically significant. This is based on the absence of an exposure-efficacy relationship and the ~2-fold range of AUC values between the 5th percentile and median in Phase 3 study 303 (Table 64).

Maribavir dose adjustments are required when coadministered with CYP3A inducer anticonvulsants carbamazepine (maribavir 800 mg BID), phenobarbital (maribavir (b) (4) BID), or phenytoin (maribavir 1,200 mg BID). These dose adjustments are based on PBPK modeling (Section III.14.4.4).

Maribavir dose adjustments are required when coadministered with CYP3A inducer anticonvulsants carbamazepine (maribavir 800 mg BID), phenobarbital (maribavir 1,200 mg BID), or phenytoin (maribavir 1,200 mg BID). These dose adjustments are based on PBPK modeling (Section III.14.4.4).

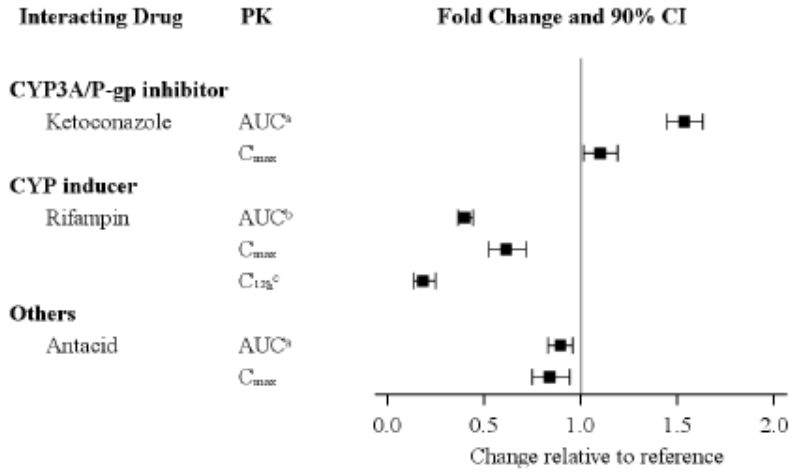
Table 63. In Vitro Studies of Maribavir as a Substrate, Inhibitor, or Inducer of Drug-Metabolizing Enzymes or Transporters

Enzyme or Transporter	Substrate	Inhibitor	Inducer
CYP1A2	Yes	Weak (IC_{50}=40 µM)	No
CYP2A6	--	No	--
CYP3A4	Yes	Weak (time-dependent; not a reversible inhibitor)	Yes
CYP3A5	No	--	--
CYP2B6	No	No	No
CYP2C8	No	No	--
CYP2C9	No	Weak (IC_{50}=18 µM)	--
CYP2C19	No	Weak (IC_{50}=35 µM)	--
CYP2D6	No	No	--
CYP2E1	--	No	--
UGT1A1/1A3/1A9/2B7	Yes	Weak (IC_{50}≥32.3 µM)	--
UGT1A4/1A6	No	No	--
P-gp	Yes	Weak (IC_{50}=33.8 µM)	--
OATP1B1/1B3	No	Weak (IC_{50}=45-50 µM)	--
BCRP	Yes	Weak (IC_{50}=7.05 µM)	--
OCT1	Yes	Weak (IC_{50}=344 µM)	--
OAT3	--	Weak (IC_{50}=33.3 µM)	--
MATE1	--	Weak (IC_{50}=20.4 µM)	--
OCT2, OAT1, MATE2K	--	No	--
BSEP	No	Weak (IC_{50}=46.5 µM)	--

BCRP=breast cancer-resistant protein; BSEP=bile salt export pump; CYP=cytochrome P450; IC_{50}=half maximal inhibitory concentration; MATE=multidrug and toxin extrusion protein; OAT=organic ion transporter; OCT=organic cation transporter; UGT=uridine diphosphate glucuronosyltransferase; P-gp=p-glycoprotein
Source: V9080M-SHP620 [VP 1264], V8537M-SHP620, V9079M-SHP620 [VP 1263], V7678M-SHP620, V8576M-SHP620, V8573M-SHP620, N11365M-SHP620 [VP 989], V7317M-SHP620, V9053M-SHP620 [VP 1334], V7676M-SHP620, V8648M-SHP620, V9052M-SHP620 [BB 1698], V7317M-SHP620.

Source: Clinical Pharmacology Summary.

Figure 5. Impact of Coadministered Drugs on the Pharmacokinetics of Maribavir



AUC=area under the plasma concentration-time curve; C_{max}=maximum observed plasma concentration; C_{trough}=observed plasma concentration at the end of a dosing interval; CYP=cytochrome P450; PK=pharmacokinetics; P-gp=P-glycoprotein

a $AUC_{0-\infty}$

b AUC_{0-t}

c C_{trough} at 12 hours post dose.

Source: Clinical Pharmacology Summary.

Table 64. Distribution of Exposures at a Maribavir Dose of 400 mg BID in Phase 3 Trial 303

```
tabstat cmaxss, stat(n min p5 p50 p95 max)
```

variable	N	min	p5	p50	p95	max
cmaxss	253	7.370552	9.848331	17.6086	33.32859	46.99698

```
tabstat aucss, stat(n min p5 p50 p95 max)
```

variable	N	min	p5	p50	p95	max
aucss	253	36.11023	55.77817	122.5681	273.2582	400.9478

```
tabstat ctrough, stat(n min p5 p50 p95 max)
```

variable	N	min	p5	p50	p95	max
ctrough	253	.2412122	1.051099	6.058447	20.38656	31.71413

Source: Reviewer's analysis. Pkefficacy.xpt dataset.
Abbreviations: AUC_{ss}, area under the curve at steady-state; BID, twice daily; C_{maxss}, peak concentration at steady-state; C_{trough}, trough concentration

8.2.2. Effects of Maribavir on Other Drugs

Based on a comparison of R values (derived from in vitro DDI studies) to the R value cutoffs, maribavir was found to be a potentially clinically relevant inhibitor of CYPs 1A2, 2C9, 2C19, 3A4, and transporters P-gp and BCRP (Table 65).

Table 65. R-Value Estimates for Inhibition of CYP Enzymes and Transporters by Maribavir and Metabolite VP 44469

Study	CYP Isozyme or Transporter	Substrate (μM)	Compound	IC_{50} (μM)	Equation[b]	R Value[c]	R Value Relative to Cutoff[d]
V9079M-SHP620 [VP 1263]	1A2	Phenacetin (25)	Maribavir[a]	40	$R_1 = 1 + (I_{max,u} / K_{i,u})$ $R_{1,gut} = 1 + (I_{gut} / K_{i,u})$	$R_1 = 1.06$ $R_{1,gut} = 292$	>1.02 >11
	2C9	Tolbutamide (140)	Maribavir	18	$R_1 = 1 + (I_{max,u} / K_{i,u})$ $R_{1,gut} = 1 + (I_{gut} / K_{i,u})$	$R_1 = 1.14$ $R_{1,gut} = 648$	>1.02 >11
	2C19	(S)-Mephenytoin (50)	Maribavir	35	$R_1 = 1 + (I_{max,u} / K_{i,u})$ $R_{1,gut} = 1 + (I_{gut} / K_{i,u})$	$R_1 = 1.07$ $R_{1,gut} = 334$	>1.02 >11
N11365M-SHP620 [VP 989]	3A4[e]	Testosterone (50)	VP 44469	30	$R_1 = 1 + (I_{max,u} / K_{i,u})$	$R_1 = 1.04$	>1.02
V9052M-SHP620 [BB 1698]	P-gp	Digoxin (10)	Maribavir	33.8	I_{gut}/IC_{50}	126	>10
V7317M-SHP620	BCRP	Cladribine (10)	Maribavir	7.05	I_{gut}/IC_{50}	603	>10
	OATP1B1	Atorvastatin (0.15)	Maribavir	45.5	$1+(f_{u,p} * I_{in,max}/IC_{50})$	1.03	<1.1
	OATP1B3	Atorvastatin (0.15)	Maribavir	49.1	$1+(f_{u,p} * I_{in,max}/IC_{50})$	1.02	<1.1
	OCT1	PAH (10)	Maribavir	344	-	-	-
	OAT3	Furosemide (5)	Maribavir	33.3	$I_{max,u}/IC_{50}$	0.03	<0.1
	MATE1	Metformin (50)	Maribavir	20.4	$I_{max,u}/IC_{50}$	0.04	<0.1
	BSEP	Taurocholic acid (1)	Maribavir	46.5	-	-	-

BCRP=breast cancer-resistant protein; BSEP=bile salt export pump; CYP=cytochrome P450; $f_{u,p}$=fraction unbound in the plasma; IC50=half maximal inhibitory concentration; I_{gut}=intestinal luminal concentration of the interacting drug; $I_{max,u}$=maximal unbound plasma concentration of the interacting drug at steady state; $I_{in,max}$=estimated maximum plasma inhibitor concentration at the inlet to the liver; $K_{i,u}$ is the unbound inhibition constant determined in vitro; MATE=multidrug and toxin extrusion protein; OAT=organic ion transporter; OATP=organic anion transporting polypeptide; OCT=organic cation transporter; P-gp=p-glycoprotein; PAH=p-aminohippurate

[a] Maribavir MW = 376.24, VP 44469 MW = 334.2.

[b] $K_{i,u}$ estimated as (IC50/2)* 0.73 (fraction of unbound drug in the human liver microsomal incubation [$f_{u,inc}$] = 0.73 [V8199M-SHP620]; $f_{u,inc}$ for VP 44469 estimated to be the same as maribavir); $I_{in,max} = I_{max} + (F_a \times F_g \times k_a \times Dose)/Q_h/R_B$

[c] Assuming steady-state maribavir geometric mean I_{max} of 17.2 μg/mL (45.7 μM; based on the final popPK report); VP 44469 I_{max} of 1.55 μg/mL (4.64 μM; based on Day 3 data from Study 1263-110); fraction unbound in the plasma ($f_{u,p}$) = 0.02 (Study V9054M-SHP620); VP 44469 $f_{u,p}$ = 0.10 (Study CMAB1002); fraction absorbed (F_a) = 0.9 (Report N10325M-SHP620); intestinal availability (F_g) = 1; absorption rate constant (k_a) = 1.29 h^{-1} (Final popPK report); hepatic blood flow rate (Q_h) = 1500 mL/min; blood-to-plasma concentration ratio (R_B) = 1.37 (Study V8198M-SHP620).

[d] Cutoff values obtained from FDA guidance: US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research [CDER]: In Vitro Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry; January 2020.

[e] VP 44469 did not inhibit the metabolism of the CYP3A4 substrates midazolam (5 μM) or nifedipine (10 μM) by ≥50% over the range tested.

Source: Studies V9079M-SHP620 [VP 1263], N11365M-SHP620 [VP 989], V9052M-SHP620 [BB 1698], V7317M-SHP620, V8199M-SHP620, V9054M-SHP620 [VP1233], V8198M-SHP620, Report N10325M-SHP620, Study CMAB1001 CSR, Study 1263-110 CSR, Final popPK report.

Source: Clinical Pharmacology Summary.

Reviewer's comment: FDA guidance recommends calculating $R_{1,gut}$ for CYP3A only. The Applicant calculated $R_{1,gut}$ for enzymes other than CYP3A but not for CYP3A. This does not impact the need for further assessment as R_1 values were exceeded for CYPs 1A2, 2C9, 2C19, and 3A4.

Clinical DDI studies were conducted with substrates of enzymes and transporters potentially inhibited by maribavir (Table 66). Maribavir did not affect the PK of warfarin, voriconazole, dextromethorphan, or midazolam.

Maribavir increased the AUC of CYP3A and P-gp substrate tacrolimus by ~50% (Table 66). Concentrations of CYP3A substrate immunosuppressants tacrolimus, cyclosporine, everolimus, and sirolimus are routinely monitored in transplant recipients. Maribavir labeling states that concentrations of these immunosuppressants should be monitored throughout maribavir treatment and to adjust the dose (based on recommendations outlined in the prescribing information of the immunosuppressant) as needed.

Maribavir increased the C_{max} of digoxin by 25% (Table 66). Digoxin labeling recommends that digoxin concentrations should be monitored when coadministered with a drug that increases

digoxin exposure <50%. Maribavir labeling states that digoxin concentrations should be monitored and the dose of digoxin may need to be reduced when coadministered with maribavir.

The effect of maribavir on the PK of BCRP substrate rosuvastatin was evaluated using PBPK modeling (III.14.4.4). An interaction cannot be ruled out. However, due to uncertainty regarding the inhibition constant for inhibition of BCRP by maribavir, the magnitude of interaction cannot be predicted with precision. Due to the potential for interaction, labeling states that when maribavir and rosuvastatin are coadministered, patients should be closely monitored for rosuvastatin-related events, especially the occurrence of myopathy and rhabdomyolysis.

Table 66. Effect of Maribavir on Coadministered Drugs

Coadministered Drug					Geometric Mean Ratio (90% CI) of coadministered drug with/without Maribavir			
Therapeutic Class	DDI mechanism	Drug Name	Dose and Frequency	N	AUC	C_{max}	C_{trough} [b]	Others
CNS Stimulants	CYP1A2 substrate	Caffeine	2 mg/kg SD	15	NA	NA	NA	0.86 (0.80, 0.92) [a]
Oral Anticoagulants	CYP2C9 substrate	Warfarin	10 mg SD	16	1.01 (0.95, 1.07) [b]	NA	NA	NA
Proton Pump Inhibitors	CPY2C19 substrate	Omeprazole	40 mg SD	16	NA	NA	NA	1.71 (1.51, 1.92) [c]
Antifungals	CPY2C19 substrate	Voriconazole	200 mg BID	19	0.93 (0.83, 1.05)	1.00 (0.87, 1.15)	NA	1.12 (1.02, 1.23) [d]
Antitussives	CYP2D6 substrate	Dextromethorphan	30 mg SD	18	0.97 (0.94, 1.00) [e]	0.94 (0.88, 1.01) [f]	NA	NA
Sedatives	CYP3A substrate	Midazolam	0.025 mg/kg IV SD	16	NA	NA	NA	1.13 (1.01, 1.24) [g]
Immunosuppressants	CYP3A/P-gp substrate	Tacrolimus	stable dose, BID (total daily dose range: 0.5-16 mg)	20	1.51 (1.39, 1.65)	1.38 (1.20, 1.57)	1.57 (1.41, 1.74)	NA
Antiarrhythmics	P-gp substrate	Digoxin	0.5 mg SD	18	1.21 (1.10, 1.32)	1.25 (1.13, 1.38)	NA	NA

AUC=area under the area under the plasma concentration-time curve; BID=twice daily; C_{max}=maximum observed plasma concentration; CYP=cytochrome P450; IV=intravenous; NA=not applicable; P-gp=P-glycoprotein; QD=once daily; SD=single dose

[a] Urine (1X+1U+AFMU)/17U concentration ratio, 0-12 h post dose.
[b] AUC ratio. for S-warfarin.
[c] Plasma omeprazole/5-hydroxyomeprazole concentration ratio, at 2 hours post dose.
[d] Voriconazole-N-Oxide/Voriconazole AUC_{0-t} ratio.
[e] Dextrorphan AUC ratio.
[f] Dextrorphan C_{max} ratio.
[g] Midazolam CL/F.

Source: Clinical Pharmacology Summary.

8.3. Plans for Pediatric Drug Development

Pediatric studies have not been initiated at this time. Of note, maribavir received an orphan drug designation on May 7, 2011, *for treatment of clinically significant CMV viremia and disease in*

at-risk patients and is therefore exempt from Pediatric Research Equity Act requirements. The Applicant was previously asked to provide their plans to study maribavir in pediatric patients and to clarify whether they are interested in receiving a Pediatric Written Request (PWR). The Applicant expressed interest in receiving a PWR for maribavir and they stated that they plan to conduct a pediatric study. They provided a synopsis (b) (4) The Division informed the Applicant that a PWR could not be based only on Trial TAK-620-2004 and that additional studies would be needed (for example, a study in patients with congenital CMV infection). Because maribavir has received an orphan drug designation and, therefore, does not trigger the Pediatric Research Equity Act, the PWR needs to be thorough and cover all possible applications of this drug in children.

In the most recent communication between the Applicant and the Division (dated October 20, 2021), the Applicant reaffirmed their interest in studying maribavir in pediatric patients in the post-transplant setting. (b) (4)

During the Advisory Committee meeting, several members of the Committee expressed the urgent need for the use of maribavir in adolescent transplant patients. Given the previous experience with drugs in other therapeutic areas for which exposures in adolescents are expected to be similar to adults, and that efficacy could be extrapolated from pivotal trial in adults, the Applicant was requested to conduct additional analysis to predict maribavir exposures for the expected weight range for adolescents. The data were reviewed by the clinical pharmacology review team who concluded that adolescents (≥12 years of age and weighing at least 35 kg) administered maribavir 400 mg BID are expected to achieve similar exposures to adults (see Section III.14.4.3). Based on these data and considering the urgent need for treatment options in adolescent post-transplant patients with CMV infection/disease that is refractory to treatment (with or without genotypic resistance) to currently available anti-CMV drugs, the multidisciplinary review team decided to extend the indication of maribavir to include adolescents (12 to 18 years of age and weighing at least 35 kg). Although safety data are not currently available for adolescents, because maribavir exposures are expected to be similar to adults, it is reasonable to assume that the safety profile would be similar as well.

8.4. Pregnancy and Lactation

The reproductive and developmental toxicology studies with maribavir are summarized in Section 7.1. In a combined fertility and embryofetal development study, maribavir was administered to male and female rats at oral doses of 100, 200, or 400 mg/kg/day. Females were dosed for 15 consecutive days prior to pairing, throughout pairing, and up to GD 17, while males were dosed 29 days prior to mating and throughout mating. A decrease in the number of viable fetuses, and increase in early resorptions and post-implantation losses were observed at ≥100 mg/kg/day (at exposures approximately half the human exposure at the RHD). Intermittent reduced body weight gain was observed in pregnant animals at ≥200 mg/kg/day. Maribavir had no effect on embryo-fetal growth or development in rats, at dose levels up to 400 mg/kg/day, at exposures similar to those observed at the RHD.

No significant toxicological effects on embryo-fetal growth or development were observed in rabbits when maribavir was administered at oral doses up to 100 mg/kg/day from GD 8 to 20, at exposures less than those at the RHD.

In the pre-and postnatal developmental toxicity study maribavir was administered to pregnant rats at oral doses of 50, 150, or 400 mg/kg/day from GD 7 to PND 21. A delay in developmental milestones was observed, including pinna detachment at doses ≥150 mg/kg/day and eye opening and preputial separation associated with reduced bodyweight gain of the offspring at 400 mg/kg/day. In addition, decreased fetal survival and litter loss was observed due to maternal toxicity and poor maternal care, respectively, at doses ≥150 mg/kg/day. No effects were observed at 50 mg/kg/day (which is estimated to be less than the human exposure at the RHD). No effects on number of offspring, proportion of males, number of live pups, or survival to PND 4 were observed at any dose in the offspring born to the second generation.

8.5. Extrinsic Factors

8.5.1. Food Effect

Food effect study 1263-104 evaluated the PK of maribavir fasted and after a meal (Section III.14.2). The meal included two eggs cooked in butter, two pieces of toast with butter, and eight ounces of whole milk. Because the meal would need to also include two strips of bacon to be considered a high fat meal per the 2019 draft FDA food effect guidance (*Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations*),[2] we consider the meal to contain moderate fat. When taken orally with a moderate fat meal versus fasted, the $AUC_{0-\infty}$ and C_{max} (geometric mean ratio [90% confidence interval] of maribavir are 0.864 [0.804, 0.929] and 0.722 [0.656, 0.793], respectively. In Phase 3 study 303, maribavir was taken with or without food and response rates were not lower in subjects with exposures in the lowest quartiles. For these reasons, we do not consider the mean ~14% lower AUC in the fed versus fasted state in study 1263-104 to be clinically significant. Labeling states that maribavir can be taken with or without food.

9. Product Quality

The Office of Pharmaceutical Quality Review team has assessed NDA 215596 with respect to Chemistry, Manufacturing, and Controls and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such the Office of Pharmaceutical Quality recommends approval of this NDA from a quality perspective.

9.1. Device or Combination Product Considerations

Not applicable.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www fda.gov/regulatory-information/search-fda-guidance-documents.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

Human Subjects Protection

The Applicant states that clinical trials were conducted in accordance with International Conference on Harmonization of Good Clinical Practice, the principles of the Declaration of Helsinki, as well as other applicable local ethical and legal requirements. The studies were reviewed and approved by the appropriate Ethics Committees and Institutional Review Boards and Informed Consent was obtained from all subjects. Trials 303 and 202 were conducted according to FDA requirements under the IND application regulations (submitted a part of IND 51001). Trial 203 was not conducted under IND 51001. Trial 203 was conducted at 38 sites in 6 European countries.

Clinical Site Inspections

At the request of the Division of Antivirals, the Office of Scientific Investigations (OSI) audited 3 sites from the pivotal Phase 3 trial (Trial 303). All 3 sites were in the United States. In addition, OSI audited 1 site from the Phase 2 Trial 203 located in Belgium. These sites were selected based on enrollment, results of the primary efficacy endpoint, and previous inspection history. On inspection of the 3 sites from Trial 303, no deficiencies were noted. At the site in Belgium from Trial 203, the primary efficacy endpoint data were verifiable and all serios adverse events were reported. However, a few adverse events in 6 subjects (all in the maribavir group) were not reported to the Applicant or FDA. Those adverse events (see Section III.20) would not have affected conclusions regarding safety. Based on the inspections of the 4 clinical sites, OSI inspectors determined that the studies were conducted adequately, and the inspectional findings support the validity and acceptability of the data as reported by the Applicant.

The Applicant Takeda was also inspected by the OSI in accordance with Compliance Program 7348.810 *Bioresearch Monitoring (BIMO) for Sponsor, CRO, and Monitors*. No issues of concern were found.

Financial Disclosure

In compliance with the rule of Financial Disclosure by clinical investigators/subinvestigators, the Applicant provided financial interest information for clinical investigators who participated in the Phase 3 trial (Trial 303) and the supportive Phase 2 trials (202 and 203. None of the clinical investigators/subinvestigators who participated in the Phase 3 trial (Trial 303) and the Phase 2 Trial 203 was employed by the Applicant or has financial interests or arrangements with the Applicant as defined in 21 Code of Federal Regulations 54.2**.**

In Trial 202 and based on the provided financial data by clinical investigators, the financial threshold was exceeded by one ((b) (6)) of 182 principle investigators/ subinvestigators. (b) (6) served as a subinvestigator for the study center (b) (6). He received payments of $40,462 for consultation and (b) (6) fees. (b) (6)

(b) (6) site enrolled (b) (6) enrolled in Trial 202; thus, it is not likely that results from one subject affected the results of the trial (see Section III.23).

11. Advisory Committee Summary

A meeting of the Antimicrobial Drug Advisory Committee of the Center for Drug Evaluation and Research of FDA was held via an online teleconference on October 7, 2021.[3] Prior to the meeting, the members of the Advisory Committee were provided with the briefing materials and slide presentations from the FDA and the Applicant.

The voting questions to the committee and the voting results are as follows:

- Is the overall benefit-risk assessment favorable for the use of maribavir for the treatment of transplant recipients with CMV infection and disease refractory to treatment and with genotypic resistance to ganciclovir, valganciclovir, foscarnet or cidofovir?

  If you voted "No," what additional information would be needed for the benefit-risk assessment to be favorable for the use of maribavir in this population?

  If a new clinical trial is recommended, please comment on trial design.

  Vote Result: Yes: 17 No: 0 Abstain: 0

Committee discussion: The Committee unanimously agreed that the overall benefit-risk assessment is favorable for the use of maribavir for the treatment of transplant recipients with CMV infection and disease refractory to treatment and with genotypic resistance to ganciclovir, valganciclovir, foscarnet, or cidofovir. The Committee members provided the following recommendations: 1) additional data post-licensing for the bone marrow transplant graft-versus-host disease population; 2) Phase 4 studies in younger adolescents, pediatric and African-American populations; 3) additional language in labelling for hematologic and renal laboratory monitoring at baseline as well as language indicating the antagonism between maribavir and ganciclovir; and 4) studies of resistance patterns, pharmacokinetics and other potential drug-drug interactions post-licensing.

- Is the overall benefit-risk assessment favorable for the use of maribavir for the treatment of transplant recipients with CMV infection and disease refractory to treatment but without genotypic resistance to ganciclovir, valganciclovir, foscarnet or cidofovir?

  If you voted "No," what additional information would be needed for the benefit-risk assessment to be favorable for the use of maribavir in this population?

  If a new clinical trial is recommended, please comment on trial design.

  Vote Result: Yes: 17 No: 0 Abstain: 0

Committee discussion: The Committee unanimously agreed that the overall benefit-risk assessment is favorable for the use of maribavir for the treatment of transplant recipients with CMV infection and disease refractory to treatment but without genotypic resistance to

[3] Please see Final Summary Minutes of the Antimicrobial Drug Advisory Committee meeting, dated October 7, 2021, to be available at: https://www fda.gov/advisory-committees/advisory-committee-calendar/october-7-2021-antimicrobial-drugs-advisory-committee-meeting-announcement-10072021-10072021.

ganciclovir, valganciclovir, foscarnet or cidofovir. The Committee members recommended post-market surveillance, therapeutic drug-monitoring, and removal of the clinical distinction between refractory disease with or without genetic resistance as it might be harmful to patients.

III. Appendices

12. Summary of Regulatory History

July 7, 1996: Investigational new drug application 051001 for maribavir was submitted in the United States by GlaxoSmithKline. Subsequently, there were several corporate entity changes over the course of maribavir's clinical development. On September 9, 2003, GlaxoSmithKline informed FDA of a change of ownership to Viropharma, Incorporated. In January 2014, Viropharma was acquired by Shire plc. Accordingly, on April 29, 2014, the Sponsor was changed to Shire-Viropharma, Incorporated. In January 2019, Shire was acquired by Takeda Pharmaceuticals. Shire is a wholly owned subsidiary of Takeda Pharmaceuticals USA, Inc. (Takeda). The investigational new drug Sponsor will remain as Shire, but the Applicant of new drug application (NDA) 215596 will be Takeda.

June 7, 2011: Maribavir received orphan designation (OD#10-3322), for the treatment of clinically significant cytomegalovirus (CMV) viremia and disease in at-risk patients.

December 15, 2017: Maribavir was granted Breakthrough Designation for the treatment of CMV infection and disease in transplant patients resistant or refractory to prior therapy.

May 3, 2018: A Type B, Initial Comprehensive Breakthrough Designation meeting was held. The meeting purpose was to discuss the overall development plan for maribavir. During the meeting, the FDA and Takeda discussed delays encountered in the enrollment of patients in the SHP620-302 trial and FDA encouraged Takeda to submit any plans for discussion that may help in expediting enrollment in Trial SHP620-302.

July 26, 2018: A Type B, Clinical Virology meeting was held to discuss and obtain the FDA concurrence on Takeda's overall approach for evaluating resistance in the maribavir Phase 3 trial, SHP620-303. The FDA recommended that Takeda submit mock datasets consistent with the human cytomegalovirus (HCMV) resistance template for feedback.

July 25, 2019: A Type B meeting was scheduled for October 8, 2019, to discuss the proposed integrated safety analysis strategy to support an NDA for maribavir as a treatment of CMV infection in transplant recipients that are resistant or refractory to prior therapy. However, the meeting was cancelled by Takeda. Takeda stated that the preliminary comments sent by the FDA on October 2, 2019, were sufficiently clear and further discussion was not required at that time.

July 27, 2020: A Type B, Clinical Virology meeting was held to discuss Takeda's proposed mitigation and analysis plan for the subset of SHP620-303 patients with a low central laboratory baseline viral load (<910 international units [IU]/mL), as assessed by the TaqMan CMV test. During the meeting, the FDA stated that any final agreement will not be reached at the meeting and additional detailed information will be required. As such, the FDA provided comments for Takeda, for which Takeda provided a response on December 14, 2020.

January 28, 2021: A Type B, Pre-NDA meeting was conducted. The purpose of the meeting was to obtain the FDA's alignment on the data package, content, and presentation for the planned NDA for maribavir. At the meeting, in general, the FDA agreed that an NDA package based on the final data from the Phase 3 Trial SHP620-303 and supportive data from the two

Phase 2 studies was acceptable for submission. The FDA agreed to the proposed content and format as well as three minor components to be submitted within 30 calendar days after the submission of the original application.

February 4, 2021: A Type B, Chemistry, Manufacturing, and Controls meeting took place. The purpose of the meeting was to discuss the data package and content pertaining to the Chemistry, Manufacturing, and Controls Sections of the planned NDA for the maribavir 200 mg tablet.

March 23, 2021: NDA 215596 was submitted to the FDA for review.

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under the IND

Selected nonclinical studies were originally submitted and reviewed under investigational new drug application 51001. All nonclinical safety studies conducted in support of maribavir were also submitted to the present NDA and are reviewed in the following sections.

13.2. Individual Reviews of Studies Submitted to the NDA

13.2.1. Pharmacology

13.2.1.1. Primary Pharmacology

Maribavir (also referred to as SRD006471, TAK-620, SHP620, VP 41263, 1263W94, BW1263W94, GW257406X) is a benzimidazole riboside antiviral drug that is being developed for treatment of post-transplant CMV infection and/or disease including in patients who are resistant and/or refractory to ganciclovir, valganciclovir, foscarnet, or cidofovir. Maribavir has a novel mechanism of action against CMV, that is mediated through inhibition of the CMV pUL97 gene product.

13.2.1.2. Secondary Pharmacology

A number of in vitro and in vivo tests were performed to identify possible off-target activity of maribavir, including its broad pharmacological effects on the central nervous system, cardiovascular system, and gastrointestinal systems, as well as on metabolic, inflammation and allergy, microbiological activity. In summary, no significant activity was observed at the dose levels and concentrations tested.

Table 67. Safety Pharmacology Studies

Study/ Study Number	Findings
M9517M-SHP620* (VP 1168): CNS function via PO CD-1 mice (4 males/group) 250, 500, and 1,000 mg/kg	At 250 mg/kg, maribavir caused hypoactivity, hypothermia, blepharospasm, and variable changes in respiratory rate; at 500 mg/kg, ataxia, tremors, diarrhea, and muscle tone decrease were observed, while at 1,000 mg/kg gasping and cyanosis preceded death. A NOAEL was not established. Additional functional motor and behavioral tests for the CNS were evaluated in mice following a single PO dose of 30, 100, or 300 mg/kg, in rats following a single PO dose of 30 mg/kg/day, or in mice and rats following a single IP dose of 30 and 10 mg/kg, respectively, in a general pharmacological screen. No significant activity was observed at the dose levels tested.
V9523M-SHP620 (VP 1521): hERG assay	At 1254 µg/mL, maribavir did not produce any significant inhibition or variation of the hERG potassium channel in HEK293 cells.
D9520M-SHP620* (VP 1504): Cardiovascular function via IV Beagle dogs (3 dogs total for cumulative dose and 3 dogs total for control) Cumulative dose of 43 mg/kg (3, 10, and 30 mg/kg was administered to each animal as an IV bolus with 30 min between each dose); vehicle was administered to control dogs	Maribavir administration to anesthetized closed-chest beagle male dogs resulted in mild changes in heart rate compared to vehicle, with no difference in mean arterial pressure. Changes were not statistically significant. In repeat-dose toxicity studies of up to 52 weeks duration in cynomolgus monkeys, maribavir had no effect on electrocardiography parameters at doses up to 180 mg/kg/day, the highest dose tested.
D9520M-SHP620* (VP 1504): Respiratory function via IV Beagle dogs (3 dogs total for cumulative dose and 3 dogs total for control) Cumulative dose of 43 mg/kg (3, 10, and 30 mg/kg was administered to each animal as an IV bolus with 30 min between each dose); vehicle was administered to control dogs	In the same study as described above, maribavir administration to anesthetized closed-chest male beagle dogs produced significant, but transient, increases (up to 2×) in respiratory rate ($p=0.002$; ANOVA) and respiratory minute volume ($p<0.001$; ANOVA).

Source: FDA reviewer
***** With the exception of the hERG study, the safety pharmacology studies were conducted prior to the introduction of ICH S7A guidance and were therefore not Good Laboratory Practice compliant.
Abbreviations: ANOVA, analysis of variance; CNS, central nervous system; HEK, human embryonic kidney; hERG, human ether-à-go-go-related gene; IP, intraperitoneally; IV, intravenous; NOAEL, no observable adverse effect level; PO, oral

13.2.1.3. ADME/PK

Table 68. Absorption, Distribution, Metabolism, and Excretion

Absorption

In vitro

- The in vitro permeability of 10µM maribavir through Caco-2 monolayers was determined in both the apical-to-basolateral (A-to-B) and basolateral-to-apical (B-to-A) directions. All samples were assayed by LC/MS. The apparent permeability was 5.6×10^{-6} cm/s and 33.7×10^{-6} cm/s in the A-to-B and the B-to-A direction, respectively. The efflux ratio was 5.7. These results indicated high absorption potential and significant efflux for maribavir in Caco-2 monolayers.

In vivo

Single-dose pharmacokinetic studies in mice, rats, and monkeys

- Oral bioavailability of maribavir was moderate to high across species at 69% in mice, 92% to 98% in rats, and 42% to 112% in monkeys.
- Systemic exposure at a low oral dose of 10 mg/kg was highest in monkeys (5.7 to 14.29 h·µg/mL) and mice (5.72 h·µg/mL) and lowest in rats (3.29 to 5.16 h·µg/mL).
- Following single IV administration, volume of distribution was high, at greater than total body water (0.7 L/kg) in all species studied (2.0 L/kg in mice, ≥1.6 L/kg in rats, and ≥9.4 L/kg in monkeys).
- In mice, clearance was moderate (1.2 L/kg/h), and in rats, rapid initial clearance (1.8 L/kg/h) was observed, followed by persistent systemic concentrations of maribavir, suggestive of enterohepatic recycling and consistent with biliary excretion being the major route of clearance of maribavir. In monkeys, clearance was approximately 0.8 L/kg/h with evidence of biliary recirculation (consistent with the rat data).

Repeat-dose toxicokinetic studies

- Repeat dose toxicokinetic evaluation was conducted for all pivotal repeat-dose toxicology studies as listed under the Toxicokinetic Studies section.

Distribution

Protein binding

- In vitro, maribavir was moderately bound to plasma proteins in mice, rats, rabbits, and monkeys at 84.7% to 93.8%, 82.7% to 88.3%, 89.7%, and 83.9% to 91.7%, respectively, and highly bound in humans at 98%). VP 44469 was less protein bound than maribavir except in rabbit plasma, where the binding was comparable (76.1%, 71.4%, 90.9%, and 78.3%, in mouse, rat, rabbit, and monkey, respectively).

Pharmacokinetics, brain penetration, oral bioavailability, and metabolism of 1263W94 in male CD-1 mice

- A preliminary study was conducted in fasted male CD-1 mice (n=2) to investigate the distribution of maribavir (10 mg/kg) into the brain following PO or IV administration. Maribavir concentrations in brain homogenate, were <5% of those in plasma at 10 minutes postdose following either route of administration.

Pharmacokinetics, distribution, and excretion of ^{14}C-maribavir following oral administration to rats

- The tissue distribution of total radioactivity was assessed in a definitive QWBA and excretion study, following single PO administration of ^{14}C-maribavir (10 mg/kg) to 7 male Sprague-Dawley (albino) and 9 male Long Evans (pigmented) rats. Quantitative whole-body autoradiography was utilized for evaluating tissue distribution of total radioactivity in intact carcasses at timepoints from 0.5 to 168 hours postdose in Sprague-Dawley rats and 0.5 to 504 hours postdose in Long Evans rats.
- Maximum concentrations of ^{14}C-maribavir-derived radioactivity in blood and plasma were observed 4 hours after PO administration, in albino rats and 0.5 hours postdose in pigmented rats.
- Levels of radioactivity declined and were not detectable in blood and plasma for both groups by 48 hours postdose.
- The blood-to-plasma concentration ratios indicated drug-related radioactivity was primarily associated with the cellular fraction of blood.
- The highest concentrations were observed in the kidney cortex, kidney, and liver.
- Other tissues with notable concentrations (>1,000 ng equivalents ^{14}C-maribavir/g) were generally in the order of kidney medulla > adrenal glands > uveal tract (pigmented) > exorbital lacrimal gland > Harderian gland > pancreas > intra-orbital lacrimal gland > small intestine > large intestine > myocardium > esophagus > salivary glands > pigmented skin (pigmented) > pituitary glands.
- High concentrations were also observed in the urine and blood.
- In pigmented rats, concentrations of radioactivity in the uveal tract were approximately 6-fold higher than those observed for albino rats, and were measurable through the last timepoint, indicating retention of DRM beyond 504 hours postdose.
- Radioactivity was also present in the pigmented skin through 72 hours postdose. These observations indicate that maribavir-related radioactivity was associated with melanin-containing tissues.

A 28-day oral range-finding toxicity study in cynomolgus monkeys given 1263W94

- The binding of maribavir to selected tissues (brain, CSF, and vitreous humor) was investigated in 1 male and 1 female monkey following administration of maribavir at oral doses of 10, 30, or 90 mg/kg twice daily (total 20, 60, or 180 mg/kg/day) in a 28-day repeat-dose toxicity study.
- Concentrations of maribavir in vitreous humor were below 1% of corresponding plasma levels. Brain concentrations ranged from about 3.5% to 20% of plasma levels.

Metabolism

In vitro

- In pooled liver microsomes and primary hepatocytes from, rats, monkeys, and humans, the primary metabolic pathways were determined as N-dealkylation of the isopropyl group to produce VP 44469 (M4), followed by glucuronidation to produce M1; direct glucuronidation of maribavir to produce three isomeric glucuronide conjugates (M7a, M7b, and M7c); N-glycosidic bond cleavage to produce M9; and by N-dealkylation and N-glycosidic bond hydrolysis to form M13 in microsomes and hepatocytes and the respective glucuronides M2/M3 and M14 in hepatocytes only.
- All pathways were represented across the species investigated and any human metabolites were also detected in rat and/or monkey.
- Glucuronidation was the primary metabolic pathway in rat and monkey hepatocytes, while human hepatocytes showed little glucuronidation, with N-dealkylation appearing to be the major metabolic pathway.
- The formation of all metabolites except M7 (both parent + glucuronide) were almost completely inhibited with the addition of ABT and tienilic acid (TA), and the formation of these metabolites were also somewhat negatively impacted by ABT and TA.
- The major metabolites of maribavir observed in vitro in human liver microsomes were also seen in vivo.

In vivo

- In vivo studies demonstrated that maribavir is primarily metabolized in the liver after systemic absorption, in mice, rats and monkeys, where it is biotransformed predominantly by CYP3A-catalyzed oxidative metabolism primarily via oxidation, N-dealkylation, N-glycosidic bond hydrolysis and glucuronidation.
- VP 44469 (N-dealkylation of the isopropyl group) has been shown to be a metabolite in mice, rats, monkeys, and the major metabolite in humans.
- The AUC ratio of VP 44469 to maribavir in human plasma has been observed between 14% and 35% (higher in moderate-severe renal impairment patients), depending on the study. See Clinical Pharmacology review for more details.
- The safety of VP 44469 (major metabolite) has been assessed based on systemic exposure in mouse, rat, and monkey repeat-dose toxicology studies. The AUC ratio of VP 44469 to maribavir in mouse, rat and monkey in pivotal toxicology studies was approximately 37%, 12% and 14%, respectively.
- Exposure multiples of VP 44469 relative to no observed adverse effect levels/lowest observed adverse effect levels in toxicology studies for C_{max} and AUC supports adequate coverage for this metabolite.

Excretion

- In vivo studies show that biliary excretion and metabolism are the major routes of elimination in mice, rats, and monkeys.
- In humans, following oral administration, maribavir is primarily eliminated by hepatic metabolism followed by urinary and fecal excretion of the metabolites.

Source: FDA reviewer
Abbreviations: ABT, 1-aminobenzotriazole; AUC, area under the curve; Caco, carcinoma, colonic; C_{max}, maximum concentration; CSF, cerebrospinal fluid; CYP, cytochrome P450; DRM, drug-related radioactive material; IV, intravenously; LC-MS, liquid chromatography-mass spectrometry; PO, oral; QWBA, quantitative whole body autoradiography

13.2.2. Toxicology

13.2.2.1. General Toxicology

A 52-Week Oral Toxicity Study in Cynomolgus Monkeys/ Study Number P9538M-SHP620/ VP1181

Key Study Findings

- A no observed adverse effect level (NOAEL) was not established in this study due to increased incidence and severity of diarrhea and soft stool (resulting in debilitation and suspension of treatment for some of the monkeys) and epithelial hyperplasia of the cecum, colon, and rectum that was observed in all treated groups. Findings reversed or were reversing following recovery.
- The lowest observed effect level (LOAEL) of 100 mg/kg/day corresponded to area under the concentration-time curve (AUC_{0-24h}) and maximum plasma concentration (C_{max}) values of 64.99 µg·h/mL and 4.52 µg/mL.
- The exposure margin was 0.25× based on human exposure after 400 mg maribavir twice daily (BID).

Conducting laboratory and location: (b) (4)

Good laboratory practice (GLP) compliance: Yes

Table 69. Methods: 52-Week Oral Toxicity Study in Monkeys

Parameter	Method Details
Dose and frequency of dosing:	0, 100, 200, 400 mg/kg/day
Route of administration:	Oral gavage
Formulation/vehicle:	Sodium citrate buffer (pH 2.2 to 2.9)
Species/strain:	Monkey/Cynomolgus
Number/sex/group:	4-8/sex/group
Age:	2 years
Satellite groups/unique design:	None
Deviation from study protocol affecting interpretation of results:	Due to continual diarrhea observed in animals at 400 mg/kg/day during the initial 10 weeks of dosing, dosing was suspended for 4 weeks and then resumed at a reduced dose of 300 mg/kg/day from Week 14. Due to continued diarrhea and severe dehydration, dosing at 400/300 mg/kg/day was discontinued in Week 32 and all surviving main group monkeys at this dose were euthanized; recovery animals 2/sex at this dose were maintained off dose for 4 weeks. Following 52 weeks of dosing, all surviving main group animals in the control, 100, and 200 mg/kg/day groups were euthanized. Recovery animals, 2/sex in the control group and 1 male and 2 females in the 200 mg/kg/day dose group, were maintained off dose for an 8-week recovery period.

Source: FDA reviewer

Table 70. Observations and Results: 52-Week Oral Toxicity Study in Monkeys

Parameter	Major Findings
Mortality	Animals were monitored for mortality twice daily. Two males at 400/300 mg/kg/day and 1 male at 200 mg/kg/day were euthanized in extremis due to diarrhea and weight loss (between Days 53 and 191).
Clinical signs	Animals were monitored for clinical signs three times daily. All doses: Diarrhea and soft stool occurred with dose-related incidence and severity throughout the study. In some animals, the continual diarrhea was associated with decreased activity, inappetence, dehydration, hunched posture, and or prolapsed rectum. As a result of these treatment-related observations, dose administration was temporarily suspended (generally for up to 2 weeks) for selected monkeys in all treatment groups.
Body weights	Body weights were recorded pre-test and weekly thereafter. With the exception of 2 males at 400/300 mg/kg/day who lost a considerable amount of weight (and were euthanized in extremis), one male at 200 mg/kg/day who showed significant weight loss during the study, and one male at 100 mg/kg/day who lost weight in the last month of dosing, all other animals maintained or slightly gained weight during the study, similarly to controls.
Ophthalmoscopy	Ophthalmoscopy was evaluated pre-test and at 3, 6, 9, and 12 months. Unremarkable
Feed consumption	Not measured
ECG	ECG was evaluated at 3, 6, 9 and 12 months. Unremarkable

Parameter	Major Findings
Hematology	Blood samples were collected pre-test and at 1, 3, 6, 9, and 12 months of study (except for the 400/300 mg/kg/day monkeys whose last collection was at 8 months of study). A number of secondary hematological alterations were considered to be the result of gastrointestinal imbalance that resulted from frequent diarrhea and dehydration (this included changes in levels of erythrocytes, hematocrit, reticulocytes, neutrophils, and lymphocytes). These changes (mostly within 10% of control values) were most pronounced in animals dosed with 400/300 mg/kg/day (HD).
Clinical chemistry	Blood samples were collected pre-test and at 1, 3, 6, 9, and 12 months of study (except for the 400/300 mg/kg/day monkeys whose last collection was at 8 months of study). HD: alkaline phosphatase was decreased by approximately 25-40% during the study. Levels returned to those observed during pretest, during the recovery period. Triglycerides were decreased but this was attributed to poor condition of the animals.
Urinalysis	Urine was collected pre-test and at 1, 3, 6, 9, and 12 months of study (except for the 400/300 mg/kg/day monkeys whose last collection was at 8 months of study). HD: Urine volume, sodium, chloride, and potassium were all decreased up to 60% at the HD, and this was attributed to the poor condition of the animals.
Gross pathology	Test article administration was discontinued for the 400/300 mg/kg/day group at the end of 8 months of study because of severe diarrhea with progression to dehydration. All survivors in this group were euthanized at this time except for 2 males and 2 females which were continued on study for a 4-week interim recovery phase, after which time they were euthanized. At the end of 1 year of test article administration, all survivors in the Control, 100, and 200 mg/kg/day group were euthanized, except for 2 monkeys/sex in the control group and 1 male and 2 females in the 200 mg/kg/day group which were continued on study for an 8-week recovery phase after which time they were euthanized. Liquid contents were observed in the cecum in some animals dosed with 100 or 200 mg/kg/day and in the colon in animals dosed with 400/300 mg/kg/day.
Organ weights	HD: Liver weights were increased by approximately 15 and 5% in males and females, respectively. This was also reflected in liver to body weight ratio.
Histopathology Adequate battery: Yes	Trace epithelial hyperplasia was noted in the cecum, colon, and rectum at all doses, which had resolved by the end of the recovery, except for epithelial hyperplasia in the cecum and colon of a single female at 400/300 mg/kg/day.

Parameter	Major Findings
Toxicokinetics Samples were collected on Day 1 and in Weeks 4, 12, 26, and 52, with the exception of animals at 300/400 mg/kg/day where no samples were obtained in Week 12 due to suspension of dosing, nor in Week 52, as all animals in this group were terminated in Week 36. Instead, toxicokinetic samples from these animals were obtained at the restart of dosing at 300 mg/kg/day in Week 14 and prior to removal from the study in Week 36.	**Table 71. Toxicokinetic Summary of Maribavir and VP 44469 in 52-Week Monkey Study** Sex-combined Exposure: Maribavir / VP 44469 Maribavir Dose (mg/kg/day): 100[a] / 200 / 400/300[b] / 100[a] / 200 / 400/300[b] C_{max} (µg/mL): 4.52[a] / 9.34 / 7.92[c] / 0.66[a] / 1.41 / 1.39[c] AUC_{0-24} (h·µg/mL): 64.99[a] / 108.37 / 95.03[c] / 9.41[a] / 18.14 / 17.52[c] AUC_{0-24}=area under the concentration-time curve from time 0 to 24 hours; C_{max}=maximum concentration; h=hour [a] Lowest-observed-adverse-effect level exposures. [b] During Week 10, dosing at 400 mg/kg/day was suspended for 4 weeks and resumed at 300 mg/kg/day. [c] Due to tolerability issues, dosing at 300 mg/kg/day was terminated after 8 months. Toxicokinetic data was collected from this group during Week 36. Source: Table 10 of the Toxicology Written Summary.

Source: FDA reviewer
Abbreviations: AD, all doses; ECG, electrocardiogram; HD, high dose

13-Week Oral Gavage Toxicity Study with VP 41263 in CD-1 Mice/ Study Number M9582M-SHP620 (BB 1596)

Key Study Findings

- The NOAEL was 150 mg/kg/day with a corresponding AUC_{0-24} 102.1 h·µg/mL and C_{max} 19.8 µg/mL, based on adverse clinical signs and mortality at 300 and 500 mg/kg/day.
- The exposure margin was 0.40× based on human exposure after 400 mg maribavir BID.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 72. Methods: 13-Week Oral Toxicity Study in Mice

Parameter	Method Details
Dose and frequency of dosing:	0, 50,150, 300,500 mg/kg/day; Daily
Route of administration:	Oral gavage
Formulation/vehicle:	Citrate buffer (0.04M) in reverse osmosis water (pH 2.6±0.3)
Species/strain:	Mouse/ CD-1
Number/sex/group:	16
Age:	7 weeks
Satellite groups/unique design:	Toxicokinetics: Additional 48 mice/sex/group Recovery: Additional 6 mice/sex/group
Deviation from study protocol affecting interpretation of results:	Due to mortality at the high dose, mice were dosed for up to 15 days (500 mg/kg main males), 17 days (500 mg/kg toxicokinetic males and females), and 71 days (500 mg/kg main females) and terminated.

Source:FDA reviewer

Table 73. Observations and Results: 13-Week Oral Toxicity Study in Mice

Parameter	Major Findings
Mortality	Animals were monitored for mortality twice daily. HD: Mortality was observed in 31 animals. Mortality was observed in both males and females in the first couple of weeks and dosing was terminated early (main and toxicokinetics animals). MD: Mortality was observed in six animals total within the first 74 days of dosing.
Clinical signs	Clinical signs were monitored twice daily; detailed observations were recorded weekly. HD: Hypoactivity in moribund animals. HD and MD: In dead or moribund sacrificed animals, clinical signs included scant feces, irregular/audible/labored respiration, clear oral discharge, rough hair coat and head tremors. In surviving animals at 300 or 500 mg/kg/day, there were clinical signs of hunched appearance, scant feces, squinted eyes, irregular respiration, clear oral discharge, and rough hair coat.
Body weights	Body weights were recorded pre-test and weekly thereafter. Unremarkable
Ophthalmoscopy	Not evaluated
Feed consumption	Food consumption was measured weekly. Unremarkable
Hematology	Blood samples were collected prior to scheduled sacrifice on Days 16 and 72 for Group 5 males and female (HD)s, respectively, and on Day 94 for Groups 1 through 4 (control, LD, LMD, MD). HD: Up to 100% increase in platelet count. HD and MD: 40-50% increase in absolute and % reticulocytes; up to 100% increase in % neutrophils; up to 25% decrease in %lymphocytes. These findings were not present in recovery animals.
Clinical chemistry	Blood samples were collected prior to scheduled sacrifice on Days 16 and 72 for Group 5 males and female (HD)s, respectively, and on Day 94 for Groups 1 through 4 (ctrl, LD, LMD, MD). HD and MD: Up to 4× increase in bilirubin. This finding was not present in recovery animals.
Urinalysis	Not evaluated
Gross pathology	Main HD animals were sacrificed after 15 and 71 days of treatment. All other main animals were sacrificed after 13 weeks of treatment. Recovery HD animals were sacrificed after 15 days of treatment and 23 weeks of recovery or after 71 days of treatment and 15 weeks of recovery. All other recovery animals were sacrificed after 13 weeks of treatment and 12 weeks of recovery. Unremarkable
Organ weights	HD and MD: test article-related increases in relative (organ-to-body) liver weights were observed in males and females, which were associated with centrilobular hepatocellular hypertrophy in males at the MD and males and females at the HD. Relative (organ-to-body) increase in spleen weights, were associated with marginal increases in severity of splenic hematopoiesis, were also noted in females at the MD. This finding were not present in recovery animals.

<table>
<tr><th>Parameter</th><th>Major Findings</th></tr>
<tr><td>Histopathology
Adequate battery: Yes</td><td>All Doses: Spleen hematopoiesis; also present in recovery animals
HD: Gastrointestinal lesions observed in 1 male and 2 females at 500 mg/kg/day were characterized by minimal to marked erosion/ulceration, mucosal hyperplasia, edema, and/or inflammation of the cecum and/or colon. In the male, minimal erosion/ulceration of nonglandular stomach was also noted, whilst slight diffuse mucosal hyperplasia of the duodenum and minimal erosion/ulceration of the glandular stomach was also noted in one of the affected females; not present in recovery animals.
MD and HD: centrilobular hepatocellular hypertrophy of the liver; not present in recovery animals

Recovery animals:
AD: Histopathology changes including chronic inflammation in the liver were observed at all doses in recovery animals, as was mucosal hyperplasia of the glandular stomach.</td></tr>
<tr><td>Toxicokinetics
Blood samples were taken on Day 1 and during Week 13 of the dosing phase predose and approximately 1, 2, 4, 8, and 24 hours postdose for animals dosed with 50, 150 or 300 mg/kg/day and approximately 4 hours postdose for control animals. For animals dosed with 500 mg/kg/day, blood samples were taken on Days 1 and 17 of the dosing phase predose and approximately 1, 2, 4, 8, and 24 hours postdose.

Samples were not collected for animals dosed with 500 mg/kg during week 13 due to early mortality at this dose</td><td>Table 74. Toxicokinetic Summary of Maribavir and VP 44469 in a 13-Week Mouse Study
<table>
<tr><th>Sex</th><th colspan="3">Male</th><th colspan="3">Female</th></tr>
<tr><th>Maribavir Dose (mg/kg/day)</th><th>50</th><th>150[a]</th><th>300</th><th>50</th><th>150[a]</th><th>300</th></tr>
<tr><th>Analyte</th><th colspan="6">Maribavir</th></tr>
<tr><td>C_{max} (µg/mL)</td><td>7.45</td><td>19.7[a]</td><td>26.7</td><td>6.93</td><td>19.9[a]</td><td>28.9</td></tr>
<tr><td>AUC_{0-24} (h·µg/mL)</td><td>34.1</td><td>99.2[a]</td><td>279</td><td>27.9</td><td>105[a]</td><td>407</td></tr>
<tr><th>Analyte</th><th colspan="6">VP 44469</th></tr>
<tr><td>C_{max} (µg/mL)</td><td>4.79</td><td>11.6[a]</td><td>19.0</td><td>2.79</td><td>6.94[a]</td><td>9.66</td></tr>
<tr><td>AUC_{0-24} (h·µg/mL)</td><td>35.0</td><td>143[a]</td><td>230</td><td>13.8</td><td>39.4[a]</td><td>145</td></tr>
</table>
AUC_{0-24}=area under the concentration-time curve from time 0 to 24 hours; C_{max}=maximum concentration; h=hour
[a] No-observed-effect level exposures
Source: Table 3 of the Toxicology Written Summary.</td></tr>
</table>

Source: FDA reviewer
Abbreviations: AD, all doses; HD, high dose; LMD, low-mid dose (150 mg/kg/day); LD, low dose; MD, mid dose

26-Week Oral Gavage Toxicity Study with VP 41263 in Rats/ Study Number R9549M-SHP620 (VP 1196)

Key Study Findings

- The NOAEL was 25 mg/kg/day with a corresponding AUC_{0-24} 12.98 and 26.75 h·µg/mL (males and females) and C_{max} 1.28 and 4.39 µg/mL (males and females), based histopathological changes observed in the gastrointestinal tract at 100 and 400 mg/kg/day.
- The exposure margin was 0.07× based on human exposure after 400 mg maribavir BID.

Conducting laboratory and location: Glaxo Wellcome Inc, United States

GLP compliance: Yes

Table 75. Methods: 26-Week Oral Toxicity Study in Rats

Parameter	Method Details
Dose and frequency of dosing:	0, 25, 100 and 400 mg/kg/day; daily (plus 28-day recovery)
Route of administration:	Oral gavage
Formulation/vehicle:	Citrate buffer (0.04M) in reverse osmosis water (pH 2.6±0.3)
Species/strain:	Rat/Wistar Han
Number/sex/group:	16-24
Age:	8 weeks
Satellite groups/unique design:	Recovery: Additional 8 rats/sex/group
Deviation from study protocol affecting interpretation of results:	None

Source: FDA reviewer

Table 76. Observations and Results: 26-Week Oral Toxicity Study in Rats

Parameter	Major Findings
Mortality	Animals were observed for mortality twice daily. HD: Mortality was observed in one male and four females. The cause of death was not established.
Clinical signs	Clinical signs were monitored twice daily; detailed observations were recorded weekly. AD: Prominent clinical signs observed during the dosing period in all treated groups included a dose-dependent increase in the incidence of salivation, typically postdose. HD and MD: Soft/mucoid feces and anogenital staining were also observed at doses ≥100 mg/kg/day, with a much higher incidence at 400 mg/kg/day. These clinical signs resolved during the postdose recovery period.
Body weights	Body weights were recorded pre-test and weekly thereafter. HD and MD: Statistically significant reductions in body weight gain (15% to 35%) without a concomitant reduction in food consumption were observed at doses ≥100 mg/kg/day. This along with reversible decreases in serum proteins and triglycerides may have been secondary to gastrointestinal distress.
Ophthalmoscopy	Ophthalmoscopy evaluation was conducted pre-test and Days 79 and 177 (control and high dose only). Unremarkable
Water consumption	Water consumption was measured on Days 177/178 and Day 26 of recovery. HD and MD: Statistically significant increased water consumption was observed.
Feed consumption	Food consumption was measured pre-test and weekly thereafter. Unremarkable

Parameter	Major Findings
Hematology	Blood samples were collected on Days 28, 84 and 178/179, 184-186, and Day 25-29 of recovery. HD: Several hematology parameters were altered: • Increased neutrophils (30 to 40%) in males and females (not observed in recovery animals) HD and MD: • Decreased eosinophils (25 to 50%) in males (data not available for recovery animals) • Platelets were increased in males and females (10 to 13%; not observed in recovery animals)
Clinical chemistry	Blood samples were collected on Days 28, 84 and 178/179, 184 to 186, and Day 25-29 of recovery. HD and MD: Several clinical pathology parameters were altered including increases in white blood cell counts (primarily neutrophils and lymphocytes), platelet counts, bilirubin (consistent with red blood cell turnover), and alanine transaminase and decreases in eosinophil counts, red blood cell counts, alkaline phosphatase, triglycerides, total protein, calcium, albumin, and globulin), at the mid and high-doses. However these changes were minimal. These findings were not present in recovery animals.
Urinalysis	Urine was collected on Days 23/25, 79/80 and 177/178 and Day 26 of recovery. HD and MD: Statistically significant increases in urinary output (likely due to increased water intake) and decreases in specific gravity, creatinine and electrolyte concentrations. Serum electrolyte concentrations were not altered, indicating no functional changes in renal function. These findings were not present in recovery animals.
Gross pathology	Animals were sacrificed on Days 184 to 186, and Day 29 of recovery. Unremarkable
Organ weights	HD: Adrenal gland weights were slightly increased in females at 400 mg/kg/day and thymus gland weights were decreased in males and females at 400 mg/kg/day. However, no microscopic correlate were observed, and these changes were considered a nonspecific response to stress. These findings were not present in recovery animals.

Parameter	Major Findings
Histopathology Adequate battery: Yes	AD: Renal cortical tubule pigment deposition was observed in both control and maribavir-treated rats with a higher incidence and severity in males at 400 mg/kg/day and females at ≥100 mg/kg/day. The incidence and severity of pigment depositions remained elevated at the end of the recovery period but did not impact renal function. Small intestine: Minimal to slight/mild mucosal hyperplasia was observed in all segments of the small intestine (duodenum, ileum, and jejunum) in males and females at 400 mg/kg/day (HD). Large intestine: Partially reversible minimal to moderate mucosal hyperplasia was observed in the cecum in females at ≥100 mg/kg/day and in males at ≥25 mg/kg/day (LD), in the colon of males and females at ≥100 mg/kg/day, and in the rectum of males and females at 400 mg/kg/day. Liver: Reversible hepatocellular cytoplasmic alterations were observed in the liver of males at doses ≥100 mg/kg/day (MD) and in females at 400 mg/kg/day (HD), which were associated with increased female liver weight at 400 mg/kg/day (HD). This finding most likely reflected induction of metabolizing enzymes as analysis of hepatic enzyme activities indicated that maribavir was a weak to moderate inducer of cytochrome P450 (CYP)1A and CYP2B activity in males and females and CYP3A activity in females. Recovery animals: Findings were partially reversible in the large intestine and fully reversible in the small intestine and liver.
Toxicokinetics Blood samples were collected on Day 1 (predose and 1, 2, 4, 8, and 24 hours postdose) and Days 35, 91, and 170 (1, 2, 4, 8, and 24 hours postdose)	**Table 77. Toxicokinetic Summary of Maribavir and VP 44469 in a 26-Week Rat Study on Day 170** **Sex** | **Males** | | | **Females** | | | **Maribavir Dose (mg/kg/day)** | **25[a]** | **100** | **400** | **25[a]** | **100** | **400** **Analyte** | **Maribavir** | | | | | | C_{max} (µg/mL) | 1.28[a] | 4.49 | 13.64 | 4.39[a] | 7.62 | 25.07 AUC_{0-24} (h·µg/mL) | 12.98[a] | 57.10 | 170.54 | 26.75[a] | 152.67 | 331.39 **Analyte** | **VP 44469** | | | | | | C_{max} (µg/mL) | 0.048[a] | 0.33 | 1.16 | 0.24[a] | 1.20 | 6.20 AUC_{0-24} (h·µg/mL) | ND | 2.00 | 18.97 | 2.98[a] | 19.28 | 107.31 AUC_{0-24}=area under the concentration-time curve from time 0 to 24 hours; C_{max}=maximum concentration; ND=not determined due to insufficient number of quantifiable samples; h=hour [a] No-observed-adverse-effect level exposures Source: Table 6 of the Toxicology Written Summary.

Source: FDA reviewer
Abbreviations: AD, all doses; HD, high dose; LMD, low-mid dose (150 mg/kg/day); LD, low dose; MD, mid dose

13.2.2.1.1. General Toxicology; Additional Studies (Non-Pivotal)

A 28-Day Oral Range-Finding Toxicity Study in Cynomolgus Monkeys Given 1263W94 / P9537M-SHP620 (VP 1178)

In a 28-day, non-GLP-compliant exploratory study, maribavir formulated in 0.5% methyl cellulose (suspension), was administered to cynomolgus monkeys (2/sex/group) at doses of 0 (control), 10, 30, or 90 mg/kg at a dose volume of 10 mL/kg BID approximately 6 hours apart (total doses of 0, 20, 60, or 180 mg/kg/day) via nasogastric intubation. One monkey/sex/group

was terminated after dosing on Day 29, and the remaining animal was maintained off dose for 39 days to assess recovery. Maribavir produced reversible changes in red blood cell parameters at 180 mg/kg/day. There were no other adverse effects and the NOAEL was 180 mg**/kg/day.**

A 30-Day Oral Toxicity Study in Cynomolgus Monkeys Given 1263W94 / P9559M-SHP620 (VP 1211); GLP

Maribavir, formulated in either citric acid/sodium hydroxide (20 or 60 mg/kg/day) or citric acid/hydrochloric acid (180 mg/kg/day), was administered to cynomolgus monkeys (3/sex/group) by oral gavage (or nasogastric) at doses of 0 (control), 10, 30, or 90 mg/kg at a dose volume of 10 mL/kg BID approximately 6 hours apart (total doses of 0, 20, 60, or 180 mg/kg/day). An additional 2 monkeys/sex were included in the control and 180 mg/kg/day groups and maintained off dose for 14 days at the end of the dosing period to assess recovery. Reversible trends in red blood cell parameters, including reductions in hemoglobin, hematocrit, and total red blood cell counts and increases in reticulocyte counts, were observed in individual animals at 60 mg/kg/day and 180 mg/kg/day. There were no other adverse effects and the NOAEL was 180 mg/kg/day.

A 26-week Oral Toxicity Study in Cynomolgus Monkeys / P9539M-SHP620 (VP 1182); GLP

Maribavir, formulated in citrate buffer approximately pH 2.4, was administered to cynomolgus monkeys (4/sex/group) by oral gavage for 26 weeks at BID doses of 0 (control), 25, 50, or 100 mg/kg at a dose volume of 10 mL/kg (total doses 0, 50, 100, or 200 mg/kg/day) for the first 3 weeks. Based on lower than anticipated systemic exposure, the doses were then doubled as of Week 4, and maribavir was administered at BID doses of 0, 50, 100, or 200 mg/kg at a dose volume of 10 mL/kg approximately 6 hours apart (total doses 0, 100, 200, or 400 mg/kg/day at a dose volume of 20 mL/kg/day) for the remainder of the study. Doses are noted as 50/100, 100/200 and 200/400 mg/kg/day below. An additional 2 monkeys/sex were included in the control and 200/400 mg/kg/day groups and maintained off dose for 4 weeks at the end of the dosing period to assess recovery.

Clinical signs, including soft/liquid feces were noted at doses ≥100/200 mg/kg starting at Week 4. One female at 100/200 mg/kg/day and 2 males and 2 females at 200/400 mg/kg/day exhibited weak condition, dehydration, reduced activity, and thin body condition associated with the abnormal feces. Due to deterioration in their condition, dosing of these animals was occasionally discontinued until they recovered, generally within 7 to 14 days, resulting in a total of between 11 to 30 off-dose days per animal. Slight reflux of the dosing material was also observed sporadically in animals in all groups, including control, with the incidence generally decreasing over the course of the study.

Reversible decreased red cell parameters (red blood cell count, hemoglobin, and hematocrit) were observed at ≥100/200 mg/kg in females and ≥200/400 mg/kg in males. This was correlated with an increase in reticulocyte counts noted at ≥100/200 mg/kg/day. A reversible decrease in urinary sodium (79% to 98%) was also observed in males during the study at doses ≥200 mg/kg/day and in females at doses ≥50/100 mg**/kg/day.**

Microscopic findings of slight to mild mucosal hyperplasia was observed at doses ≥50/100 mg/kg/day in the cecum and colon, and at doses ≥100/200 mg/kg/day in the rectum,

which had resolved by the end of the recovery period except in 1 female at 200/400 mg/kg/day where slight mucosal hyperplasia was still present in the rectum.

VP 44469 exposure values were approximately 16% those of maribavir.

The LOAEL was 50/100 mg/kg/day based on adverse clinical signs of soft/liquid feces and histopathology findings of mucosal hyperplasia in the large intestine at all dose levels. This corresponded to maribavir sex-combined C_{max} and AUC_{0-24} values of 2.97 μg/mL and 41.07 h·μg/mL.

14-Day Oral Gavage Dose Range-Finding Toxicity Study with VP 41263 in CD-1 Mice / M9583M-SHP620 (VP 1597)

In a non-GLP-compliant, 14-day, dose range-finding study, maribavir, formulated in a citric acid (0.04M) buffer in reverse osmosis water (pH 2.6±0.3), was administered by oral gavage at a volume of 10 mL/kg to CD-1 mice (4/sex/group) at doses of 0 (control), 250, 350, or 500 mg/kg/day once daily for 7 days after which doses were doubled to 500, 700, and 1,000 mg/kg/day for the remaining 7 days of dosing. Doses are noted as 250/500, 350/700, and 500/1,000 mg/kg/day below. No test article-related adverse clinical signs were observed during the first 7 days of dosing; thus, the doses were doubled for planned administration from Day 8 to Day 14. Based on mortality in mice at doses ≥700 mg/kg/day during the second week of dosing (clinical signs in mice that died included irregular respiration, ataxia, hypoactivity, squinted eyes, cold to the touch, rough hair coat, and recumbency), 500 mg/kg/day was considered to be the maximum-tolerated dose. Although no test article-related clinical signs were observed in animals given 500 mg/kg/day during the first week of dosing, the animals given 250/500 mg/kg/day did exhibit test article-related signs during the period when they were given 500 mg**/kg/day.**

Dose Range Finding Toxicity Study of 1263W94 Given by Gavage to HSD Rats for 28 Days / R9554M-SHP620 (VP 1205)

In an initial non-GLP-compliant exploratory dose range-finding study, maribavir, formulated in 0.5% methylcellulose, was administered once daily by oral gavage at a volume of 10 mL/kg to Sprague-Dawley rats (4/sex/group) at doses of 0 (control), 100, 200, or 400 mg/kg/day. Mild anemia characterized by decreased hemoglobin, hematocrit, and red blood cell counts was observed at the highest dose of 400 mg/kg/day. The NOAEL was 200 mg/kg/day based on mucosal hyperplasia in the cecum at 400 mg/kg/day. Humans do not have a cecum so the relevance of these findings is unclear.

30-Day Oral Toxicity Study in Sprague-Dawley Rats With a 17-Day Recovery Period / R9568M-SHP620 / VP 1225; GLP

Ten male and female Sprague-Dawley rats per group (plus 5/sex/group in the control and high dose for 17-day recovery and 12/sex/group for toxicokinetics evaluation) were dosed with vehicle (citric acid buffer solution with hydrochloric acid (0.1 N)) or 100, 200 or 400 mg/kg/day maribavir.

Clinical signs were observed in all groups (salivation and altered feces; resolved during recovery), and at ≥200 mg/kg (anogenital staining; resolved during recovery).

Test article-related hematological changes included increases in total white blood cell, monocyte and reticulocyte counts, and whilst being broadly within test laboratory historical limits, were dose related in incidence, being observed predominantly in males and females at 200 mg/kg/day and 400 mg/kg/day. Additionally, increases in neutrophil counts were noted in both males and females at 400 mg/kg/day and 1 female at 100 mg/kg/day. Most of the hematological changes resolved during the recovery period, with the exception of absolute neutrophil and monocyte counts in 1 female at 400 mg/kg/day. Increases in total bilirubin (up to 75%) observed in females at 200 mg/kg/day and 400 mg/kg/day resolved during postdose recovery. Increases in absolute and relative adrenal weights (in both males and females) were noted at all doses. In females only, increased spleen weights were observed at all doses and slight increases in liver weights were observed at 200 mg/kg/day and 400 mg/kg/day. Whilst no histopathological corelates were observed, the increase in spleen weight may have been due to increased erythropoiesis. These changes had resolved by the end of the recovery period, with the exception of liver weights in 3 out of 5 females at 400 mg/kg.

Gross findings at necropsy included minimal to moderate distension of the cecum with mucoid discolored contents observed in a subset of animals at all doses, and moderate distension of the duodenum and colon noted in isolated animals. Histological findings were present in the cecum, colon, duodenum spleen and liver of both sexes. Mucosal hyperplasia in the cecum (very slight to slight) and colon (very slight) and duodenal villous hyperplasia were observed at all doses. In addition, in the colon there was a reduction in mucosal cell numbers. Very slight to moderate splenic erythropoiesis was observed at all doses which may have contributed to the very slight increases in erythropoietic foci observed in the liver at 400 mg/kg/day, with a higher incidence in females. There was a complete resolution of all histological findings at the end of the recovery period. Increases in systemic exposure were approximately proportional to dose across the dose range, with higher exposure in females than in males and some evidence of accumulation on repeated dosing. Based on the adverse finding of mucosal hyperplasia in the gastrointestinal tract at all doses, a NOAEL was not identified in the study. The LOAEL was 100 mg/kg/day at which maribavir C_{max} values of 3.62 µg/mL and 7.50 µg/mL and AUC_{0-8} values of 54.3 h·µg/mL and 106.3 h·µg/mL were achieved in males and females, respectively. See Table 78.

Table 78**. Genetic Toxicology**

Study/Study Number	Key Study Findings
In Vitro Reverse Mutation Assay in Bacterial cells/V9578M-SHP620 (VP 1503) GLP compliance: Yes Study is valid: Yes	Cytotoxic effects: Toxicity of the test compound towards the tester strains in the absence and presence of S9, was seen in the preincubation modification only, manifested as a reduction in the background bacterial lawn at 650 µg/plate. This therefore precluded further evaluation of the results at this concentration in the preincubation modification only. Genotoxic effects: Maribavir was found to be non-mutagenic with tester strains TA1535, TA1537, TA98, TA100 and TA102 in the absence and presence of S9 at concentrations up to and including that of 650 µg/plate in the Ames test and 205 µg/plate in the pre-incubation modification. Each strain responded to the positive direct and pro-mutagen controls with the required increases in reversion rate. The response with the direct mutagen was at least twice the spontaneous reversion rate in the presence and absence of S9. The pro-mutagen caused an increase of at least twice the spontaneous reversion rate in the presence of S9 only, with the response in the absence of S9 being consistent with the spontaneous reversion rate. According to the study report, some data points for spontaneous reversion of strains or response to positive controls were not within historical limits. These historical limits were subject to revision and it was the opinion of the Study Director that they did not invalidate the test results.
Preliminary study L5178Y/tk+/- Mouse Lymphoma Mutagenesis Study with 1263w94/ M9571M-SHP620 (VP 1230) GLP compliance: Yes Study is valid: Yes	Mouse lymphoma L5178Y cells; up to 200 µg/mL; +/-S9 Cytotoxic effects: The maximum concentration that could be tested both in the absence and presence of exogenous mammalian metabolic activation was 200 µg/mL due to the cytotoxic effects of the compound. Genotoxic effects: Maribavir was not mutagenic in the presence of S9. However, in the absence of metabolic activation, the test results were considered equivocal; neither the positive nor the negative evaluation criteria was met.
Exploratory study VP 41263: 1263W94UH: Mammalian Cell Mutation Test at the Thymidine Kinase Locus in Mouse Lymphoma L5178Y Cells/M9572M-SHP620 (VP 1271) GLP compliance: Yes Study is valid: Yes	Mouse lymphoma L5178Y cells; up to 200 µg/mL; -S9 Cytotoxic effects: In the absence of rat liver S9-mix, in the first test, no cells survived above concentration of 200 µg/mL and relative survival rate was reduced to 70% and 6% at 100 and 200 µg/mL, respectively. In the second test, relative survival rate was more gradual at 46%, 17%, 6%, and 0.9% at the concentration of 125, 150, 175, and 200 µg/mL, respectively. Genotoxic effects: Maribavir was weakly mutagenic in the mouse lymphoma test system in the absence of an in vitro metabolic activation system (rat liver S9-mix).

Study/Study Number	Key Study Findings
Expanded protocol study VP 41263: 1263W94: Mammalian Cell Mutation Test At the Thymidine Kinase Locus in Mouse Lymphoma L5178Y Cells/ M9535M-SHP620 (VP 1170) GLP compliance: Yes Study is valid: Yes	Mouse lymphoma L5178Y cells; up to 200 µg/mL; +/-S9 Four tests in total were carried out; two in the absence of S9 (5 µg/mL to 150 µg/mL) and two in the presence of S9 (5 µg/mL to 200 µg/mL). Cytotoxic effects: In the absence of rat liver S9-mix, no cells survived in the treatment at the maximum concentration of 150 µg/mL and relative survival was reduced to less than 10% at 50 and 75 µg/mL. In the presence of rat liver S9-mix, relative survival was reduced to less than 10% at 150 and 200 µg/mL and poor cellular growth occurred throughout the expression period at 100 µg/mL. Genotoxic effects: Maribavir demonstrated mutagenic potential in the mouse lymphoma test system in the absence of an in vitro metabolic activation system (rat liver S9-mix), and no conclusive evidence of mutagenic potential was observed in the presence of S9-mix.
Assay for Micronucleus Induction in Rat Bone Marrow From an Oral Toxicity Study/R9556M-SHP620 (VP 1208) GLP compliance: Yes Study is valid: Yes	Rat, bone marrow micronuclei; single oral doses of 400, 800 or 1,200 mg/kg via oral gavage; bone marrow sampled 24 and 48 hours postdose. There was no cytotoxic or cytostatic effect on erythroblast proliferation. Analysis of plasma samples taken from rats dosed 1,200 mg/kg demonstrated detectable circulating levels of test material 4 hours after being dosed (male rats 6.45-12.06 µg/mL, female rats 10.89-13.28 µg/mL) which confirmed exposure. Cyclophosphamide, the positive control, induced the expected increase in micronucleated polychromatic erythrocytes (MPCE) establishing the validity of the assay. Vehicle control was 0.04M citrate buffer (pH 2.55) as a solution of citric acid in 0.1 N sodium hydroxide.
Other genetic toxicology studies	None

Study/Study Number	Key Study Findings
Expert opinion	Two expert opinion reports were provided. Expert Report 1 Weak increases in mutant frequency were observed at cytotoxic dose levels in mouse lymphoma 51 78Y tk locus studies in the absence of an exogenous mammalian metabolic activation. The presence of exogenous metabolic activation reduced or eliminated the activity. Analysis of mutant colony size suggests that the increases in mutant frequency in the mouse lymphoma assays were primarily due to increases in small colonies which are considered to reflect clastogenic chromosome damaging processes. The rat micronucleus assay would be an appropriate assay for detecting such effects in vivo. Consideration of all of the genotoxicity test results using a weight of evidence approach leads to the conclusion that the genotoxicity profile does not indicate significant in vivo mammalian genotoxic potential for 1263W94. Expert Report 2 The required test battery was performed, and the mouse lymphoma assay without metabolic activation yielded a positive response. The Salmonella and bone marrow assays were clearly negative. Based on the mouse lymphoma assay colony sizes, the response did not appear to be the result of preferential increases in large or small colonies, which indicates that there was no preferential induction of gene or chromosomal mutations. It is important to note that the loss of the weak mouse lymphoma response, and the cytotoxicity, when metabolic activation (S9) was used is an indication that the test substance will be inactivated in vivo. This is supported by the lack of effect seen in the in vivo micronucleus test at blood plasma levels of the test chemical that were equivalent to the concentrations that were positive in the mouse lymphoma test. It is not clear what an additional assay would offer. The overall sensitivities and predictivities of the DNA elution and UDS tests are not well documented and appear to be low. If the results in these tests were negative it would not negate the implications of the weak positive mouse lymphoma assay, or aid in its interpretation. If they were positive, there are insufficient data to support any conclusions about carcinogenicity. The in vivo bone marrow test was performed at plasma concentrations equivalent to those that produced the weak positive response in vivo, and was negative. The rodent cancer assay in two species is already in progress. As a consequence, there is nothing to be gained by performing an additional genetic toxicity test.

Source: FDA Reviewer
Abbreviations: DNA, deoxyribonucleic acid; GLP, good laboratory practice UDS, unscheduled DNA synthesis

13.2.2.2. Carcinogenicity

104-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with Maribavir in CD-1 Mice/ M9526M-SHP620 (BB 1710)

The carcinogenicity potential of maribavir was tested in an oral 2-year mouse carcinogenicity study. CD-1 mice were administered 25, 75, or 150 mg/kg/day of maribavir formulated in 0.04M citrate buffer in water (pH 2.6±0.3) daily via oral gavage for 104 weeks. Two identical control groups received the vehicle only.

Although the FDA Statistical Reviewer determined statistical significance for the incidence of adenocarcinomas in the uterus of female mice at 150 mg/kg/day, this finding was considered negative because it did not meet the statistical criteria for significance for a common tumor (this tumor occurred at >1% in historical controls). The Executive Carcinogenicity Assessment Committee concurred that this was a negative finding.

The FDA Statistical Reviewer's tumor analysis showed trend (p=0.0002) and pairwise (p=0.0006) statistically significant increases in whole body hemangiosarcoma and combined hemangioma/hemangiosarcomas in male mice observed at the high dose of 150 mg/kg (see Statistics review). The Executive Carcinogenicity Assessment Committee concurred that this was a positive finding.

As such, there were no test article related neoplastic or non-neoplastic findings in this study at up to 75 mg/kg/day ($AUC_{0\text{-}24h}$ 90 and 6,305 µg·h/mL, males and females, respectively), corresponding to exposures 0.35 and 0.25 times the exposure observed at the recommended human dose.

104-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with Maribavir in Han Wistar Rats/ R9581M-SHP620 (VP 1570)

The carcinogenicity potential of maribavir was tested in an oral 2-year rat carcinogenicity study. Wistar Han rats were administered 10, 30 or 100 mg/kg/day of maribavir formulated in 0.04M citrate buffer in water (pH 2.6±0.3) daily via oral gavage for 104 weeks. Two identical control groups received the vehicle only. There were no variations of tumor incidences considered related to administration of maribavir based on the FDA statistical review. The NOAEL in the study was 100 mg/kg/day after 2 years of daily oral administration of maribavir. At Week 52 of the dosing phase, the dose of 100 mg/kg/day corresponded to an $AUC_{0\text{-}Last}$ value of 92.6 µg·h/mL in females and 50.1 µg·h/mL in males. In general, systemic exposure to VP 44469 (metabolite) was below the level of quantification on most sampling occasions.

The Executive Carcinogenicity Assessment Committee concurred that this study was negative.

As such, there were no test article related neoplastic or non-neoplastic findings in this study at up to 100 mg/kg/day ($AUC_{0\text{-}24h}$ 50.1 and 92.6 µg·h/mL, males and females, respectively), corresponding to exposures 0.20 and 0.36 times the exposure observed at the recommended human dose.

13.2.2.3. Reproductive and Developmental Toxicology

13.2.2.3.1. Fertility and Early Embryonic Development

Maribavir: Oral Fertility and Embryo-Fetal Development Study in the Han Wistar Rat/ R9558M-SHP620 (VP 1210)

Key Study Findings

- A NOAEL for reproductive endpoints was not established due to increased incidence of pre-and post-implantation loss in females and a decrease in sperm straight-line velocity in males at all doses. The LOAEL was 100 mg/kg which corresponded to a C_{max} of 9.57 µg/mL and $AUC_{0\text{-}24h}$ of 126.74 µg·h/mL on gestation day 17 in females.

- The NOAEL for maternal toxicity was 100 mg/kg, based on reduced weight gain and decreased food consumption.
- The exposure margin was 0.5× based on human exposure after 400 mg maribavir BID.

Conducting laboratory and location: Glaxo Wellcome Research and Development Ware, Hertfordshire UK (main study) and Glaxo Wellcome, Research Triangle Park, United States (toxicokinetics/formulation analysis)

GLP compliance: Yes

Table 79. Methods: Oral Fertility and Embryo-Fetal Development Study in Female and Male Rats

Parameter	Method Details
Dose and frequency of dosing:	Untreated, 0 (vehicle), 100, 200 or 400 mg/kg; daily
Route of administration:	Oral gavage
Formulation/vehicle:	Solutions equivalent to 10, 20, or 40 mg/mL in 0.04M citrate buffer, pH adjusted to pH 2.3 to 3.0
Species/strain:	Rat, Wistar Han, Crl:WI(Han)
Number/sex/group:	24/sex/group
Satellite groups:	None
Study design:	Females: 15 days prior to mating, throughout mating and until Day 17 of pregnancy Males: 29 days prior to mating, throughout mating and until necropsy (Days 70 and 72)
Deviation from study protocol affecting interpretation of results:	No

Source: FDA reviewer

Table 80. Observations and Results: Oral Fertility and Embryo-Fetal Development Study in Female and Male Rats

Parameter	Major Findings
Mortality	Five animals were euthanized due to dosing error.
Clinical signs	Salivation and loose feces were observed in all treated groups
Food consumption	HD and MD: A transient reduction in food consumption in both sexes was observed in the first seven days of treatment (decrease of 9% to 18%)
Body weights	HD: Reduced body weight was observed in males at 400 mg/kg/day (decrease of 40%) HD and MD: Reduced gestation body weight gain (up to 57%) was observed between gestational Days 4 and 8, and Days 15 and 18.
Sperm count	HD: Low sperm count as compared to control; not considered toxicologically significant because only 1 male (out of 20) was lower than the historical control.
Sperm velocity	HD: Sperm straight-line velocity was decreased at all doses
Necropsy findings (mating/fertility index, corpora lutea, preimplantation loss, etc.)	• Embryofetal survival in utero was impaired at all doses with mean pre- and post-implantation losses of between 13.7% to 18.1% and 6.7% to 9.0%, respectively, compared to control values of 6.8% and 3.7%, respectively. • Early resorptions were increased at ≥200 mg/kg/day • No fertility effects were observed. • No test article-related fetal skeletal or visceral abnormalities or variants were observed.
Toxicokinetics Blood samples were collected 1.5 h postdose on the first and twelfth day of dosing. Samples were also taken on Day 17 of pregnancy, at four time points per female from the following times:- 1, 2, 4, 6, 8, 24, 28 and 32 h postdose (a total of two samples per time point per group)	**Table** 81**. Toxicokinetic Parameters for Maribavir in Rat** Fertility and Embryo-Fetal Development Study; GD 17 **Sex: Females** **Maribavir Dose (mg/kg/day): 100[a] / 200 / 400** C_{max} (µg/mL): 9.57[a] / 15.27 / 23.04 AUC_{0-24} (h·µg/mL): 126.74[a] / 233.11 / 280.01 AUC_{0-24}=area under the concentration-time curve from time 0 to 24 hours; C_{max}=maximum concentration; GD=gestational day; h=hour [a] No-observed-adverse-effect level exposures. Source: Table 10 of the Toxicology Written Summary

Source: FDA reviewer
Abbreviations: HD, high dose; MD, mid dose

13.2.2.3.2. Embryo-Fetal Development

Maribavir: Oral Embryofetal Development Study in New Zealand White Rabbits/ L9541M-SHP620 (VP 1187)

Key Study Findings

- The NOAEL (maternal and developmental) in this study was 100 mg/kg/day (highest dose), with a maternal AUC_{0-24} value of 114.16 µg·h/mL and C_{max} of 23.05 µg/mL.
- The exposure margin was 0.45× based on human exposure after 400 mg maribavir BID.

Conducting laboratory and location: Glaxo Wellcome Research and Development Ware Hertfordshire UK (main study) and Glaxo Wellcome, Research Triangle Park, United States (toxicokinetics/formulation analysis)

GLP compliance: Yes

Table 82. Methods: Oral Embryo-Fetal Developmental Study in Rabbits

Parameter	Method Details
Dose and frequency of dosing:	0, 25, 50 or 100 mg/kg/day
Route of administration:	Oral gavage
Formulation/vehicle:	0.04M Citrate buffer (nominal pH range 2.2 to 2.7)
Species/strain:	New Zealand White Rabbit
Number/sex/group:	22 females per group
Satellite groups:	None
Study design:	Dosing GD 8 to GD 20
Deviation from study protocol affecting interpretation of results:	No

Source: FDA reviewer
Abbreviation: GD, gestation day

Table 83. Observations and Results: Oral Embryo-Fetal Developmental Study in Rabbits

Parameters	Major Findings
Mortality	At the HD of 100 mg/kg/day, one rabbit was euthanized on GD 13 and one was found dead on GD 14. Both were attributed to gavage errors.
Clinical signs	Unremarkable
Body weights	Unremarkable
Necropsy findings Cesarean section data	Unremarkable
Necropsy findings Offspring	Unremarkable
Toxicokinetics Blood samples were collected predose and at approximately 1, 3 and 6 h after dosing on the first and last day of treatment (Days 8 and 20 of pregnancy, respectively).	**Table** 84**.** Toxicokinetic Parameters for Maribavir in Rabbit EFD Study; GD 8 and 20

Gestational Day	GD 8			GD 20		
Maribavir Dose (mg/kg/day)	25	50	100[a]	25	50	100[a]
C_{max} (µg/mL)	4.36	6.99	23.87[a]	5.43	9.23	23.05[a]
AUC_{0-24} (h·µg/mL)[b]	11.54	20.23	87.88[a]	38.16	36.89	114.16[a]

AUC_{0-24}=area under the concentration-time curve from time 0 to 24 hours; C_{max}=maximum concentration; GD=gestational day; h=hour

[a] No-observed-adverse-effect level exposures.

[b] AUC_{0-24} was extrapolated, assuming that the 24-hour samples had the same exposures as 0-hour samples.

Source: Table 17 of the Toxicology Written Summary

Source: FDA reviewer
Abbreviations: GD, gestation day; HD, high dose

13.2.2.3.3. Prenatal and Postnatal Development

Maribavir: Oral Pre- and Postnatal Study in the Han Wistar/ R9555M-SHP620 (VP 1206)

Key Study Findings

- The NOAEL for parental and first filial generation was 50 mg/kg (low dose) based on:
  - Parental: Maternal toxicity at ≥150 mg/kg and resulting decrease in first filial survival and increased incidence of litter losses.
  - First filial: Delays in development at ≥150 mg/kg/day and reduced body weight gain at 400 mg/kg/day.
  - Limited toxicokinetic assessment was conducted.
- The NOAEL for the second filial generation was 400 mg/kg (highest dose).

Conducting laboratory and location: Glaxo Wellcome Inc., Research Triangle Park, North Carolina, United States

GLP compliance: Yes

Table 85. Methods: Oral Pre- and Post-Natal Developmental Toxicity Study in Rats

Parameter	Method Details
Dose and frequency of dosing:	0, 50, 150, 400 mg/kg/day
Route of administration:	Oral gavage
Formulation/vehicle:	0.04M citrate buffer pH 2.2 to 2.9
Species/strain:	Rat/ Wistar Han
Number/sex/group:	24 females per group
Satellite groups:	None
Study design:	Females were dose from GD 7 to PPD 21; F0 females were euthanized on PPD 21; 1 male and 1 female offspring selected to form F1 generation; F1 generation allowed to mate and go through gestation and parturition; F1 and offspring (F2) euthanized on PPD 4
Deviation from study protocol affecting interpretation of results:	No

Source: FDA reviewer
Abbreviations: F0, parental; F1, first filial; F2, second filial; GD, gestation day; PPD, postpartum day

Table 86. Observations and Results: Oral Pre- and Post-Natal Developmental Toxicity Study in Rats

Generation	Major Findings
F0 generation (dams)	HD: Loose feces and decreased body weight gain during lactation (observed up to PND 8). HD and MD: Mortality, loose feces (HD only) clinical signs including postdose salivation, fur staining, loud breathing, and lip licking; decreased food consumption and decreased weight gain during pregnancy.
F1 generation	HD: Delay in the onset of eye opening and preputial separation, which were associated with the reduction in pup body weight gain at 400 mg/kg/day. HD and MD: Decreased fetal survival due to maternal (F0) toxicity and increase in total litter loss by PND 8 due to lack of maternal care; delay in onset of pinna detachment (associated with reduced pup weight observed at HD only).
F2 generation	Unremarkable; no effect of maribavir on number of offspring, proportion of males, number of live pups, or survival to PND 4.

Source: FDA reviewer
Abbreviations: F0, parental; F1, first filial; F2, second filial; HD, high dose; MD, mid dose; PND, postnatal day

Juvenile Toxicology Studies

- Maribavir was evaluated in three 4-week juvenile toxicity studies in rats: an exploratory study (R10949M-SHP620) and two follow-up GLP studies (R11007M-SHP620, and R11521M-SHP620).
- In the exploratory and first pivotal studies, an age-dependent increase in exposure was observed in younger pups.
  - As a result, in the second pivotal study, doses were adjusted based on the age of pups to maintain a steady exposure in animals in the low- and high-dose groups.
  - This was generally achieved, although there were still significant but smaller differences between exposures based on age, despite the dose adjustment, as compared to the first pivotal study.
- In all the juvenile toxicity studies the rats were dosed from PND7-PND34, followed by 2 weeks or 1 month of postdose recovery; juvenile rats were dosed up to 300/225 mg/kg/day (males/females) in pivotal studies.
- There were no significant maribavir-related findings in the GLP studies, and the highest doses tested were the study NOAELs.
- Exposures in juvenile studies reached up to 389 µg·h/mL (AUC_{0-24}) and 23.6 µg/mL (C_{max}).

13.2.2.4. Other Toxicology Studies

Table 87. Other Toxicology Studies

Immunotoxicity/ R9525M-SHP620 (BB 1697) 0, 5, 15 or 50 mg/kg maribavir BID for 7 days via oral gavage	Maribavir did not adversely affect the immune system as evidenced by no changes in immunoglobulin antibody response to the T-dependent antigen and sheep red blood cells in the spleen at dosages up to 100 mg/kg/day in Sprague-Dawley rats. Maribavir was also evaluated for the potential to produce immunotoxicity in standard toxicity studies. A review of the rat and monkey studies of up to 26 weeks and 52 weeks, respectively, did not reveal any effects suggestive of immunomodulation.
Phototoxicity/ V8722M-SHP620	Maribavir was not phototoxic in a neutral red uptake study in embryonic albino Swiss mouse fibroblasts at concentrations of 1.78, 3.16, 5.62, 10.0, 17.8, 31.6, 56.2, and 100 µg/mL. Half-maximal inhibitory concentration values (-UVR or +UVR) could not be calculated, indicating that maribavir did not show cytotoxicity or phototoxicity in this assay.
Dermal toxicity / R9557M-SHP620 (VP 1209), G9527M-SHP620 (VP 1115), L9543M-SHP620 (VP 1189) Up to 2000 mg/kg in Wistar Han rat (topical) Up to 1% w/v intradermal induction, 50% w/w topical induction and up to 50% w/w topical challenge in Dunkin-Hartley guinea pigs Up to 500 mg topical patch in New Zealand White rabbits	Maribavir was not a dermal irritant in rats, skin sensitizer in guinea pigs or dermal irritant in rabbits.
Ocular toxicity / L9542M-SHP620 (VP 1188) 10 mg or 0.1 mL (57 mg) of maribavir into the conjunctival sac of the right eye of New Zealand White rabbits	Maribavir was considered as a slight ocular irritant at 10 mg and corrosive at 57 mg in rabbits.

Source: FDA reviewer
Abbreviations: BID, twice daily, UVR, ultraviolet radiation

Impurity Studies

There are currently 3 specified impurities in the maribavir drug substance specifications: (b) (4) (the Stage 1 product), (b) (4) (the Stage 2 product), and (b) (4) .

- However, none of these impurities have been detected in any large-scale batches manufactured since 2012.
- Historically, (b) (4) was listed as a specified impurity, but it was removed in 2015.
- During development, studies were performed to identify and evaluate risk associated with synthetic and degradation impurities (actual and potential) to support the use of the

selected API starting materials. Actual and potential degradation products were not observed in the product.

All actual and potential impurities for the maribavir process (33 total) were assessed according to International Conference on Harmonisation (ICH) M7(R1) for potential mutagenicity using literature data and in-silico screening software (Derek Nexus and Leadscope).

- Compounds that were potentially mutagenic per in-silico assessment (b) (4) were further assessed via the use of the bacterial reverse mutation (Ames) tests.
  - All Ames test results for the impurities listed above were negative.
- Of the 33 compounds assessed in the in-silico assessment, only (b) (4) was classified as Class 1 under ICH M7(R1).
  - (b) (4) is a known mutagenic carcinogen with positive results in multiple mammalian and bacterial genetic toxicity assays. Furthermore, this structure has been shown to be positive in male and female mice and rats for carcinogenicity.
  - A compound-specific intake limit was calculated in accordance with ICH M7(R1). This limit was calculated based on a 2-year feeding study conducted in male and female (b) (4) mice and (b) (4) rats afforded median toxic dose values of (b) (4) mg/kg/day in mice and (b) (4) mg/kg/day in rats, respectively.
  - According to Note 4 of ICH M7(R1), linear extrapolation to a probability of 1 in 100,000 (i.e., the accepted lifetime risk level used) is achieved by simply dividing the median toxic dose by 50,000. In this respect, the most sensitive point of departure is the median toxic dose of (b) (4) mg/kg/day determined for the tumor formation in the urinary bladder and forestomach in rats.
  - The corresponding compound-specific tolerable intake for (b) (4) according to the calculation method outlined in ICH M7(R1), would be (b) (4) µg/kg/day.
  - However, the California Environmental Protection Agency found the no significant risk level for (b) (4) according to the approach described above using the same carcinogenicity study as point of departure, is (b) (4) µg/day or approximately (b) (4) µg/kg/day assuming a standard body weight of 70 kg. Considering the refined approach followed by the California Environmental Protection Agency as compared to the linear back-extrapolation outlined in ICH M7(R1), the no significant risk level of (b) (4) µg/kg/day represents a more conservative and evidence-based tolerable daily intake level associated with no significant cancer risk. In conclusion, (b) (4) µg/day or (b) (4) µg/kg/day (b) (4) is considered the most sensitive and evidence-based tolerable daily intake level associated with no significant cancer risk and is recommended in line with Note 4 of ICH M7(R1).
  - A limit of less than (b) (4) µg/day corresponds to a (b) (4) parts per million limit for (b) (4) based on the maximal daily dose of 800 mg of maribavir.
- No non-mutagenic related impurities have been observed in the drug substance at a level above the ICH Q3A(R2) reporting threshold and therefore are not considered to have an impact on the impurity profile of the drug substance.

14. Clinical Pharmacology: Additional Information and Assessment

14.1. In Vitro Studies

Protein Binding

Protein binding of maribavir 0.05 to 20 µg/mL in human plasma was evaluated using equilibrium dialysis (V9054M-SHP620 [VP 1233]). The mean percent bound was 98.0% and was independent of concentration at concentrations <50 µg/mL (mean C_{max} at the therapeutic dose of 400 mg BID in transplant patients was 17 µg/mL).

Maribavir ex vivo plasma protein binding ranged from 98.5 to 99.0% in clinical studies CMAB1001, CMAB1002, 1263-101, 1263-103, and 1263-200, and was independent of population (healthy, renal or hepatic impairment, transplant).

Blood to Plasma Partitioning

Human whole blood samples were used to measure red blood cell partitioning of maribavir (V8198M-SHP620). Maribavir mean (standard deviation) blood to plasma ratio was estimated to be 1.37 (0.13).

Metabolism

The conversion of maribavir to the N dealkylated metabolite (VP 44469) was assessed for cytochrome P450 (CYP) 1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 metabolism (V8537M-SHP620). Incubation of maribavir in human liver microsomes and recombinant CYPs resulted in the formation of 1 major metabolite by N dealkylation (VP 44469) and 2 minor metabolites: M9 formed by N glycosidic cleavage and M13 formed by N dealkylation and N glycosidic bond hydrolysis. Based on recombinant CYPs, CYP3A4 intrinsic clearance was estimated to be 0.05 µL/min/pmol with a contribution of 66.4%, while CYP1A2 intrinsic clearance was estimated as 0.06 µL/min/pmol with a contribution of 33.6%.

Maribavir as a Substrate, Inhibitor, and Inducer of Drug-Metabolizing Enzymes and Transporters

See Table 63 and Table 65.

14.2. In Vivo Studies

Conclusions drawn from in vivo studies, such as labeling statements, are discussed in Sections II.8.1 and II.8.2.

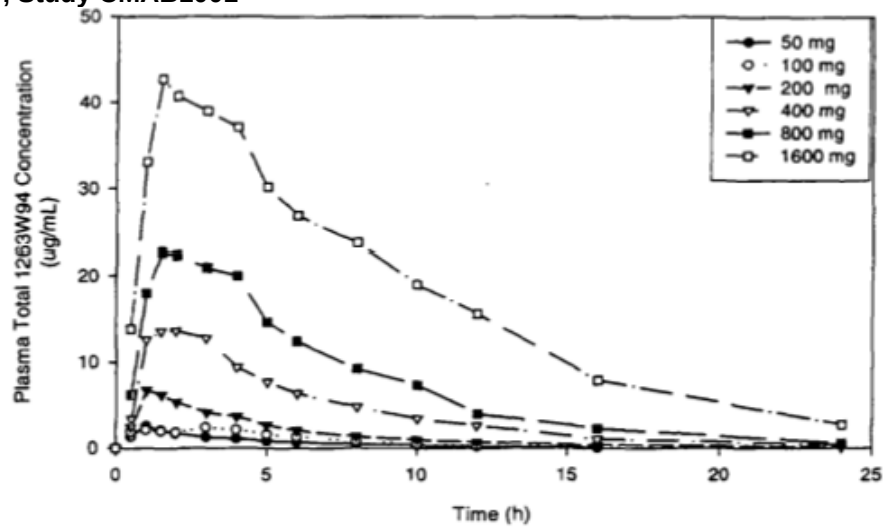
Single Ascending Dose

Study CMAB1001 evaluated a single dose (placebo and 50, 100, 200, 400, 800, and 1,600 mg) of maribavir capsules in healthy volunteers (n=12, n=10 for maribavir; n=2 for placebo). Subjects were dosed under fasted conditions, with a 1-week washout between each treatment.

Blood and urine samples were collected through 24 hours postdose for measurement of maribavir and VP 44469 concentrations. Unbound fraction was measured at the 200 mg and 800 mg dose levels.

Maribavir and VP 44469 exposures increased approximately dose proportionally from 50 to 1,600 mg. The metabolic ratio (MR) for VP 44469, calculated as the ratio of $AUC_{0-\infty}$ of VP 44469/molecular weight of VP 44469 (334.2) to $AUC_{0-\infty}$ of maribavir/molecular weight of maribavir (376.24), ranged from 0.15 to 0.20. <2% of maribavir was excreted unchanged in the urine. VP 44469 accounted for 30 to 40% of the dose in urine. Maribavir mean plasma protein binding was 99%. See Figure 6.

Figure 6. Mean Plasma Maribavir Concentration-Time Data Following Oral Administration of Maribavir, Study CMAB1001



Note: Maribavir referred to as 1263W94 in this figure.
Source: Study CMAB1001 CSR, Section 14, Table 3

Table 88. Single-Dose Maribavir and VP 44469 Pharmacokinetic Parameters in Healthy Subjects, Study CMAB1001

	Maribavir Dose (mg)					
Parameter	50 (N=10)	100 (N=10)	200 (N=10)	400 (N=10)	800 (N=10)	1600 (N=10)
Maribavir						
AUC_{0-t} (µg*h/mL)	10.31 (32.51)	15.92 (28.36)	33.27 (47. 14)	95.45 (27.35)	171.83 (30.86)	413.43 (33.47)
$AUC_{0-\infty}$ (µg*h/mL)	10.77 (31.76)	16.31 (27.49)	34.16 (49.42)	97.80 (29.23)	183.05 (37.74)	436.75 (37.42)
C_{max} (µg/mL)	2.66 (20.92)	3.32 (36.82)	7.45 (38.82)	16.68 (34.29)	26.39 (25.95)	48.81 (16.14)
T_{max} (h)	1.00 (0.50, 1.50)	2.26 (0.50, 5.00)	1.26 (1.00, 4.00)	1.75 (1.00, 3.00)	1.50 (1.02, 4.20)	2.00 (1.00, 3.00)
$t_{1/2}$ (h)	3.28 (18.61)	3.01 (15.44)	3.64 (29.98)	3.91 (20.04)	4.04 (25.24)	4.80 (31.95)
CL/F (L/hr)[a]	5.02 (27.90)	6.46 (20.70)	6.69 (30.40)	4.39 (27.21)	4.84 (31.10)	4.12 (35.69)
Fe (%)	0.59 (21. 63)	0.67 (54.73)	0.78 (41.46)	0.68 (24.00)	1.50 (27.22)	1. 56 (27.58)
CL_r (L/h)[a]	0.029 (32.43)	0. 043 (57.21)	0.055 (57.40)	0.031 (37.21)	0.072 (31.43)	0.066 (40.11)
VP 44469						
AUC_{0-t} (µg*h/mL)	1. 27 (29.20)	2.34 (19.42)	5. 30 (16.94)	14.27 (26.49)	23.05 (24.40)	51.29 (15.48)
$AUC_{0-\infty}$ (µg*h/mL)	1. 85 (33.95)	2.90 (13.16)	6.02 (18.06)	16.23 (31.79)	27.49 (20.54)	60.01 (22.05)
C_{max} (µg/mL)	0.19 (24.21)	0.32 (25.21)	0.65 (35.29)	1.37 (35.14)	2.11 (27.83)	3.64 (15.57)
T_{max} (h)	1.50 (1.00, 4.00)	3.00 (1.00, 6.00)	2.01 (1.02, 5.00)	3.00 (1.02, 5.00)	3.00 (2.00, 5.00)	4.00 (3.00, 12.00)
$t_{1/2}$ (h)	6.31 (46.37)	4.96 (13.84)	5.23 (27.58)	5.95 (20.51)	6.65 (50.75)	7.18 (42.81)
Fe (%)	28.45 (23.01)	31.94 (22.84)	32.54 (33.89)	29.49 (17.99)	42.20 (17.87)	35.56 (19.52)
CL_r (L/h)[a]	9.14 (37.19)	11.72 (25.50)	11.57 (27.85)	8.58 (26.04)	14.24 (24.36)	11.45 (29.44)

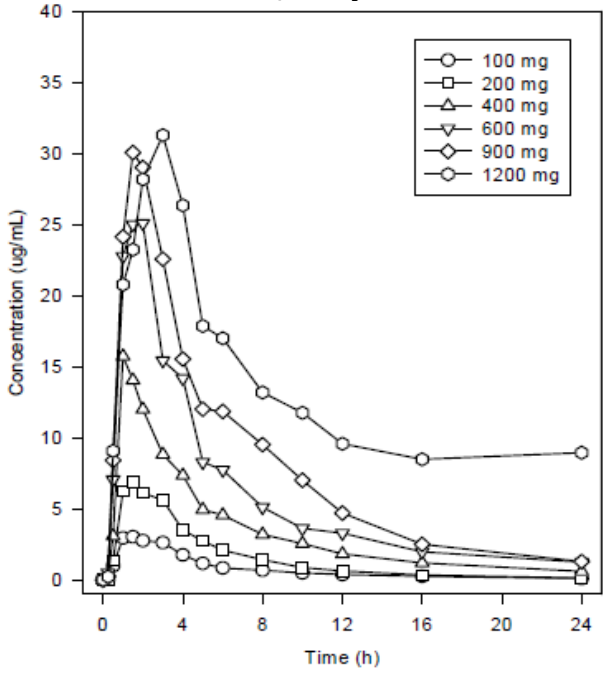
AUC_{0-t}= area under the plasma concentration vs time curve from time 0 to the last measurable concentration; $AUC_{0-\infty}$=area under the plasma concentration vs time curve from time 0 to infinity; CL/F=oral clearance; CLr=renal clearance; C_{max}=maximum observed plasma drug concentration; Fe=percent of dose recovered; $t_{1/2}$=terminal half-life; T_{max}=time to maximum observed plasma drug concentration
[a] CL/F and CLr units were converted from mL/min to L/h.
Note: All values presented as mean (%CV) except T_{max}, which is presented as median (min, max).
Source: Study CMAB1001 CSR Section 14, Table 5, Table 10

Multiple Ascending Dose

Study CMAA1003 evaluated the single and multiple dose pharmacokinetics (PK) of maribavir capsules in human immunodeficiency virus (HIV)-infected men. Subjects were randomized to receive 28 days of dosing of placebo or maribavir (100, 200, or 400 mg thrice daily [TID], or 900 or 1,200 mg BID). Administration with regard to food was not specified in the protocol. Blood and urine samples were collected through 24 hours postdose for measurement of maribavir and VP 44469 concentrations.

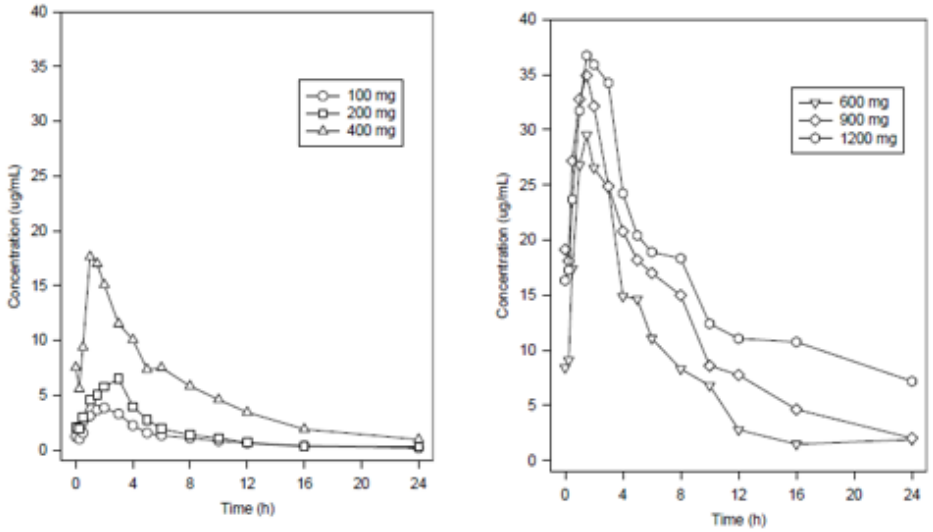
Maribavir exposures increased approximately dose proportionally over the dose range evaluated. The Day 1 to Day 28 maribavir AUC ratio ranged from 1.20 to 1.52. The Day 28 $AUC_{0-\tau}$ /Day 1 $AUC_{0-\infty}$ ratios were all close to 1 (0.97 to 1.13) across the BID and TID cohorts, indicating PK of maribavir was time-independent. <5% of the dose was excreted as unchanged maribavir in urine. See Figure 7, Figure 8, and Table 89.

Figure 7. Mean Plasma Maribavir Concentration-Time Data on Day 1 Following Single Oral Administration of Maribavir, Study CMAA1003



Source: Study CMAA1003 CSR Section 10, Table 10.2.2.1.2, Table 10.2.2.1.3, Table 10.2.2.1.4, Table 10.2.2.1.5, Table 10.2.2.1.6, Table 10.2.2.1.7

Figure 8. Mean Plasma Maribavir Concentration-Time Values on Day 28 Following Oral Administration of Maribavir, Study CMAA1003



Source: Study CMAA1003 CSR Section 10, Table 10.2.2.1.9, Table 10.2.2.1.10, Table 10.2.2.1.11, Table 10.2.2.1.12, Table 10.2.2.1.13, Table 10.2.2.1.14

Left panel: 100, 200, and 400 mg maribavir thrice daily
Right panel: 600, 900, and 1,200 mg twice daily

Table 89. Single-Dose (Day 1) and Multiple-Dose (Day 28) Maribavir Pharmacokinetic Parameters, Study CMAA1003

Parameter	Maribavir Dose (mg)					
Day 1	**100 (N=11)**	**200 (N=12)**	**400 (N=10)**	**600 (N=7)**	**900 (N=12)**	**1200 (N=10)**
$AUC_{0-\tau}$ (µg*h/mL)[a]	12.79 (43.42)	28.79 (58.2)	55.49 (33.91)	122.01 (26.14)	154.82 (33.75)	206.05 (49.01)
$AUC_{0-\infty}$ (µg*h/mL)	18.24 (50.83)	36.18 (61.55)	85.25 (51.28)	164.66 (55.22)	196.78 (48.93)	309.86 (65.31)
C_{max} (µg/mL)	3.783 (40.64)	8.154 (51.65)	18.102 (40.11)	30.551 (31.43)	35.366 (22.10)	34.005 (44.06)
T_{max} (h)	1.5 (0.5, 3.0)	1.75 (1.0, 3.0)	1.5 (1.0, 4.0)	2.0 (1.0, 2.0)	1.5 (1.0, 3.0)	2.5 (1.0, 3.0)
$t_{1/2}$ (h)	5.07 (35.56)	4.55 (34.95)	5.86 (46.13)	5.23 (62.39)	5.04 (27.95)	6.39 (43.21)
CL/F (L/h)	7.4 (66.21)	8.57 (73.69)	5.97 (55.63)	4.35 (38.78)	5.33 (35.78)	6.51 (97.08)
Fe (%)	1.43 (42.41)	1.21 (48.42)	1.49 (61.44)	2.98 (80.02)	1.90 (41.68)	2.47 (70.49)
Day 28	**100 TID (N=11)**	**200 TID (N=6)**	**400 TID (N=9)**	**600 BID (N=5)**	**900 BID (N=8)**	**1200 BID (N=9)**
$AUC_{0-\tau}$ (µg*h/mL)[a]	17.2 (43.38)	26.73 (51.38)	77.42 (28.31)	126.76 (26.7)	229.92 (44.85)	249.0 (50.74)
$AUC_{0-\infty}$ (µg*h/mL)	26.43 (58.23)	34.28 (58.55)	121.12 (42.13)	222.93 (75.55)	302.05 (56.82)[c]	285.72 (32.35)
C_{max} (µg/mL)	4.371 (40.23)	6.999 (39.14)	19.189 (27.21)	33.499 (41.30)	43.532 (37.85)	43.905 (38.410)
T_{max} (h)	2.0 (1.0, 3.0)	1.75 (1.0, 3.0)	1.5 (1.0, 2.0)	1.5 (1.0, 3.0)	1.5 (0.5, 3.0)	1.5 (1.0, 4.0)
$t_{1/2}$ (h)	5.67 (54.01)	3.78 (33.86)	5.37 (22.76)	6.10 (51.67)	4.73 (31.25)	5.83 (39.14)[c]
CL/F (L/h)	7.34 (65.6)	9.81 (66.45)	5.63 (33.25)	4.01 (63.94)	4.81 (51.13)	5.96 (53.05)
Day 28 $AUC_{0-\tau}$/ Day 1 $AUC_{0-\infty}$	1.015 (26.46)[d]	0.970 (37.30)	1.099 (40.0)	1.117 (33.8)[e]	1.057 (49.08)	1.129 (83)
Rac[b]	1.407 (28.86)	1.198 (41.36)[f]	1.523 (32.41)	1.240 (30.84)[g]	1.493 (44.94)[g]	1.465 (62.81)
Fe(%)	1.75 (83.79)	0.93 (48.43)[c]	1.98 (112.38)[d]	4.24 (110.71)	2.97 (58.56)[h]	2.67 (67.9)

AUC_{0-t}= area under the plasma concentration vs time curve from time 0 to the last measurable concentration; AUC_{0-8}=area under the plasma concentration vs time curve from time 0 to 8 hours; AUC_{0-12}=area under the plasma concentration vs time curve from time 0 to 12 hours; $AUC_{0-\infty}$=area under the plasma concentration vs time curve from time 0 to infinity; CLr=renal clearance; C_{max}=maximum observed plasma drug concentration; Fe=fraction excreted unchanged in the urine; NA=not applicable; Rac=accumulation ratio; $t_{1/2}$=terminal half-life; T_{max}=time of maximum plasma drug concentration

[a] $AUC_{0-\tau}$ = AUC_{0-8} for TID cohorts and $AUC_{0-\tau}$ = AUC_{0-12} for BID cohorts.

[b] Rac calculated as Day 28 $AUC_{0-\tau}$/ Day 1 $AUC_{0-\tau}$.

[c] N=8.

[d] N=10.

[e] N=3

[f] N=5.

[g] N=7.

[h] N=9.

Note: All values presented as mean (%CV) except T_{max}, which is presented as median (min, max).

Source: Study CMAA1003 CSR Section 10,Table 10.2.2.4.1, Table 10.2.2.4.2, Table 10.2.2.4.3, Table 10.2.2.4.4, Table 10.2.2.4.5, Table 10.2.2.4.6, Table 10.2.2.4.7, Table 10.2.2.4.8, Table 10.2.2.4.9, Table 10.2.2.4.10, Table 10.2 2.4.11, Table 10.2.2.4.12

Mass Balance and Metabolite Profiling

Study 1263-106 evaluated a single maribavir dose of 400 mg oral solution via nasogastric tube in six fasted healthy subjects. Blood, urine, and feces were collected through 144 hours postdose dose for measurement of maribavir and VP 44469 concentrations. See Figure 9 and Table 90.

Mean (range) recovery of the radiolabeled dose:

- Total: 75% (59 to 88)
- Urine: 61% (52 to 70)
- Feces: 14% (6 to 23)

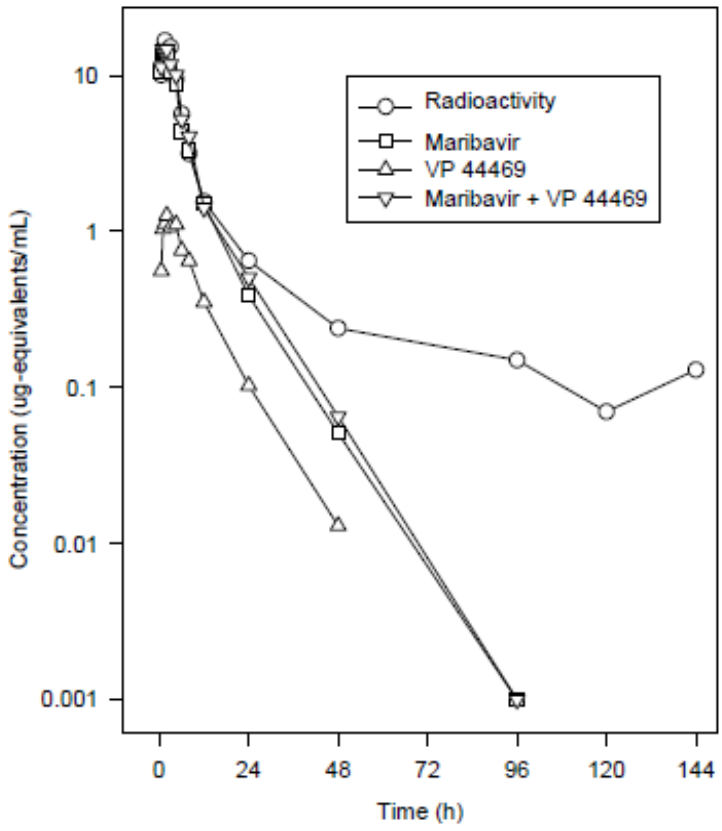
Percent of the dose recovered:

- Maribavir: 1.8% in urine and 5.7% in feces
- VP 44469: 34% in urine and 7.2% in feces

For the first 24 hours after drug administration, the radioactivity observed in plasma consisted of maribavir (88%) and VP 44469 (12%).

Six metabolites (M1 to M6) were identified in urine. VP 44469 (M4) was the primary metabolite in urine and feces.

Figure 9. Mean Plasma Total Radioactivity, Maribavir, VP 44469, and Maribavir + VP 44469 Concentrations Following Administration of a 400 mg Solution of [^{14}C]-Maribavir, Study 1263-106



Source: Study 1263-106 CSR Section 10, Table 10.2.1.1, Table 10.2.1.2, Table 10.2.1.3, Table 10.2.1.4

Values are in mar bavir-equivalent concentrations, µg/mL

Table 90. Summary of PK Parameters of the Total Plasma Radioactivity, Maribavir, VP 44469, and Maribavir Plus VP 44469, Study 1263-106

Parameter	Total Radioactivity (in µg-equivalents of Maribavir) (N=6)	Maribavir (N=6)	VP 44469 (N=6)	Maribavir + VP 44469[a] (N=6)
AUC_{0-24} (µg*h/mL)	95.9 (28.4)	84.8 (40.8)	11.6 (11.0)	97.7 (34.3)
AUC_{0-t} (µg*h/mL)	119.1 (21.8)	89.1 (44.0)	12.6 (8.4)	103.3 (37.5)
$AUC_{0-\infty}$ (µg*h/mL)	130.0 (22.5)	89.3 (43.9)	12.8 (7.9)	103.5 (37.4)
C_{max} (µg/mL)	19.8 (32.0)	16.3 (23.6)	1.3 (22.6)	17.7 (21.3)
T_{max} (h)	1.8 (1, 3)	1.5 (1,3)	2.0 (1.5, 4.5)	1.5 (1, 3)
$t_{1/2}$ (h)	65.79 (101.7)	6.42 (29.2)	6.96 (21.8)	NA

AUC_{0-t}= area under the plasma concentration vs time curve from time 0 to the last measurable concentration; AUC_{0-24}= area under the plasma concentration vs time curve from time 0 to 24 hours; $AUC_{0-\infty}$=area under the plasma concentration vs time curve from time 0 to infinity; C_{max}=maximum observed plasma drug concentration; Kel=elimination rate constant; NA=not applicable; $t_{1/2}$=terminal half-life; T_{max}=time of maximum plasma drug concentration; Vz/F= oral terminal-phase distribution volume

[a] Expressed as µg-equivalents of maribavir.

Note: All values presented as mean (%CV) except T_{max}, which is presented as median (min, max).

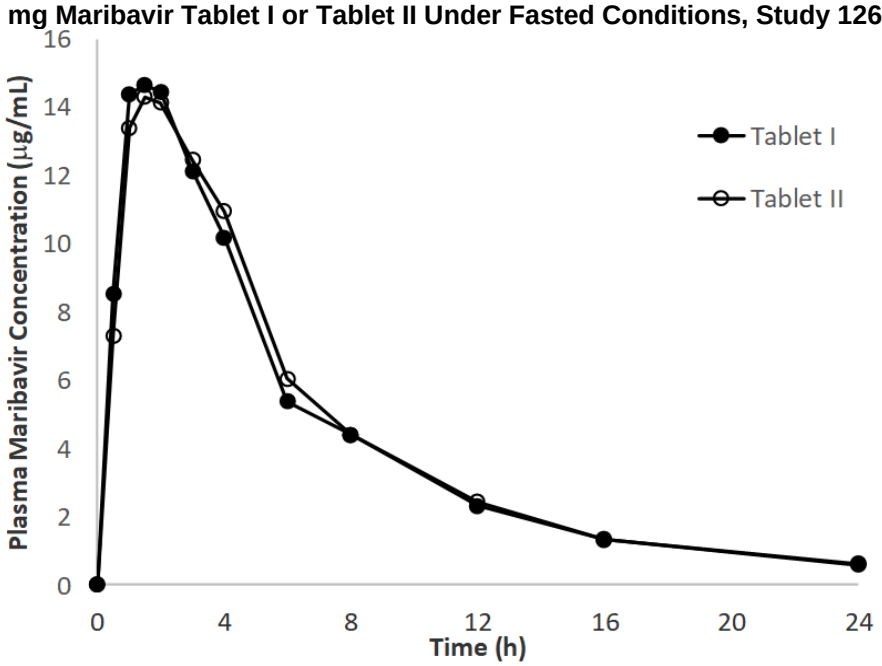
Source: Study 1263-106 CSR Section 10, Table 10.2.3.1, Table 10.2.3.2, Table 10.2.3.3; Table 10.2.3.4

Food Effect (and Relative Bioavailability of Tablets)

The relative bioavailability of tablets (I and II) and food effect (tablet II) were evaluated in 28 healthy adults in study 1263-104. Subjects received the following three treatments separated by one-week washout periods: Tablet I fasted; Tablet II fasted; and Tablet II after ingestion of a moderate fat breakfast (two eggs cooked in butter, two pieces of toast with butter, and eight ounces of whole milk) of unspecified total calories. Blood samples were collected through 24 hours postdose for measurement of maribavir plasma concentrations.

There was no difference in C_{max} or AUC between the formulations. Relative to the fasted state, administration with food resulted in geometric mean 14% lower maribavir AUC and 28% lower C_{max}. See Figure 10 and Table 91, and Figure 11 and Table 92.

Figure 10. Mean Plasma Maribavir Concentrations Following a Single Oral Administration of 400 mg Maribavir Tablet I or Tablet II Under Fasted Conditions, Study 1263-104



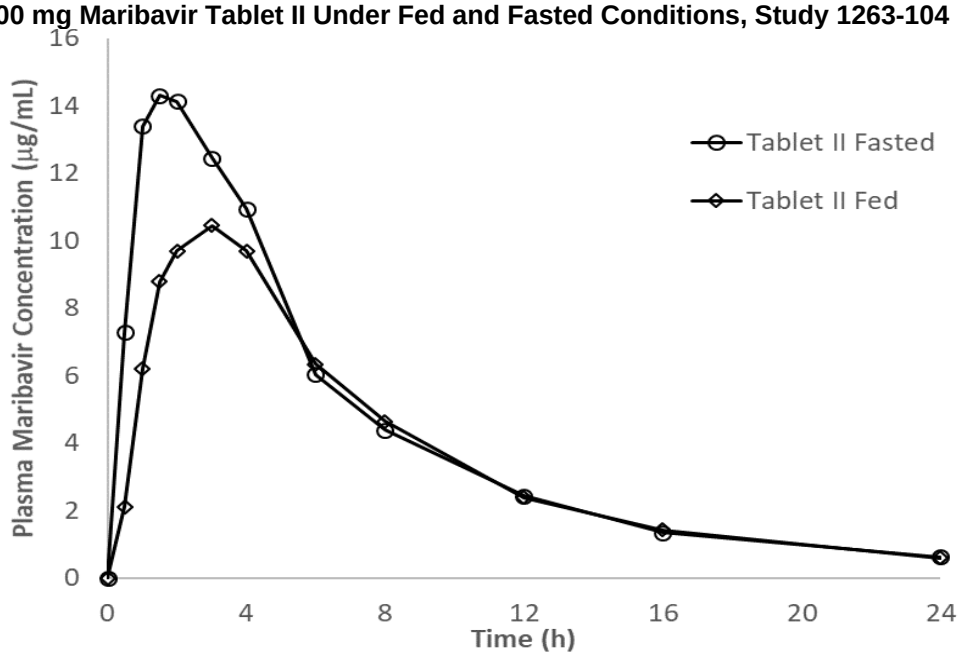
Source: Study 1263-104 CSR, Table 10.2.1.1, and Table 10.2.1.2

Table 91. Statistical Analysis of the Pharmacokinetic Parameters of Maribavir Following a Single Oral Dose of 400 mg Maribavir Tablet I or Tablet II Under Fasted Conditions, Study 1263-104

Parameter	Tablet II (N=29)	Tablet I (N=28)	Tablet II/Tablet I[a] (90% CI) (N=28)
AUC_{0-t} (µg*h/mL)[b]	95.0	91.8	1.038 (0.968, 1.114)
$AUC_{0-\infty}$ (µg*h/mL)[b]	99.0	95.6	1.040 (0.968, 1.118)
C_{max} (µg/mL)[b]	15.9	16.5	0.964 (0.887, 1.059)
T_{max} (h)[c]	1.5 (1.0, 4.0)	1.5 (0.5, 4.0)	N/A[d]

ANOVA=analysis of variance; AUC=area under the plasma concentration-versus-time curve from time 0 to the last measurable concentration (AUC_{0-t}) and from time 0 to infinity ($AUC_{0-\infty}$); CI=confidence interval; C_{max}=maximum measured plasma concentration; N/A=not applicable; T_{max}=time to C_{max}.
[a] Least squares geometric mean ratio
[b] Geometric mean
[c] Median (minimum, maximum)
[d] The p-value for the ranked values of T_{max} from the ANOVA model was 0.858.
Source: Study 1263-104 CSR, Table 10.2.3.1, Table 10.2.3.2, and Table 10.2.3.4.

Figure 11. Mean Plasma Maribavir Concentrations Following a Single Oral Administration of 400 mg Maribavir Tablet II Under Fed and Fasted Conditions, Study 1263-104



Source: Study 1263-104 CSR, Table 10.2.1.2 and Table 10.2.1.3

Table 92. Statistical Analysis of the Pharmacokinetic Parameters of Maribavir Following a Single Oral Dose of 400 mg Maribavir Tablet II Under Fed and Fasted Conditions, Study 1263-104

Parameter	Tablet II Fed (N=29)	Tablet II Fasted (N=29)	Tablet II Fed / Tablet II Fasted[a] (90% CI) (N=28)
AUC_{0-t} (µg*h/mL)[b]	81.6	95.0	0.860 (0.802, 0.922)
$AUC_{0-\infty}$ (µg*h/mL)[b]	85.6	99.0	0.864 (0.804, 0.929)
C_{max} (µg/mL)[b]	11.4	15.9	0.722 (0.656, 0.793)
T_{max} (h)[c]	2.0 (1.0, 4.0)	1.5 (1.0, 4.0)	N/A[d]

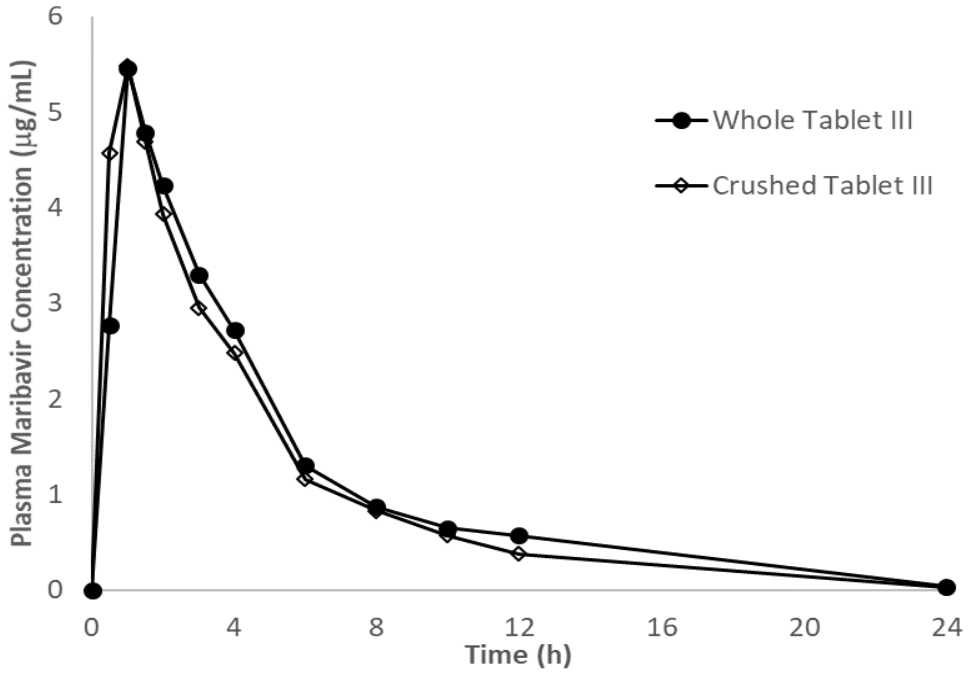
ANOVA=analysis of variance; AUC=area under the plasma concentration-versus-time curve from time 0 to the last measurable concentration (AUC_{0-t}) and from time 0 to infinity ($AUC_{0-\infty}$); CI=confidence interval; C_{max}=maximum measured plasma concentration; N/A=not applicable; T_{max}=time to C_{max}.
[a] Least squares geometric mean ratio
[b] Geometric mean
[c] Median (minimum, maximum)
[d] The p-value for the ranked values of T_{max} from the ANOVA model was <0.001.
Source: Study 1263-104 CSR, Table 10.2.3.2, Table 10.2.3.3, and Table 10.2.3.4.

Relative Bioavailability of Whole and Crushed Tablets

Study 1263-109 evaluated a single dose of maribavir 100 mg (Tablet III) taken whole, crushed, or taken whole 10 minutes after an antacid (800 mg aluminum hydroxide and 800 mg magnesium hydroxide). Fifteen healthy volunteers received each of the treatments separated by 1-week washout periods. Blood and urine samples were collected through 24 hours postdose for measurement of maribavir and VP 44469 concentrations.

There was no difference in PK parameters when administered as whole versus crushed tablets. When taken with an antacid versus alone, geometric mean maribavir C_{max} was 16% lower and AUC 11% lower. See Figure 12 and Table 93, and Figure 13 and Table 94.

Figure 12. Mean Plasma Maribavir Concentrations Following a Single Oral Administration of Maribavir Whole or Crushed 100 mg Tablet III, Study 1263-109



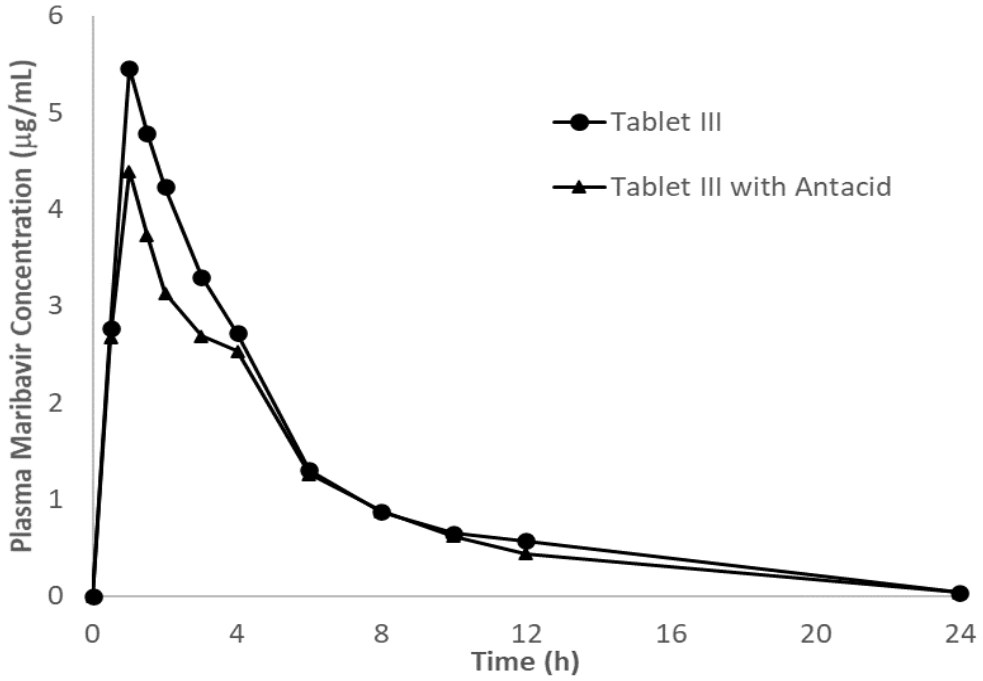
Source: Study 1263-109 CSR, Table 10.2.1.1 and Table 10.2.1.2

Table 93. Statistical Analysis of the Pharmacokinetic Parameters of Maribavir Following a Single Oral Dose of Maribavir Whole or Crushed 100 mg Tablet III, Study 1263-109

Parameter	Crushed Tablet III (N=15)	Whole Tablet III (N=15)	Crushed Tablet III/Whole Tablet III[a] (90% CI) (N=15)
AUC_{0-t} (µg*h/mL)[b]	21.4	22.1	0.971 (0.903, 1.043)
$AUC_{0-\infty}$ (µg*h/mL)[b]	23.4	24.3	0.960 (0.892, 1.033)
C_{max} (µg/mL)[b]	5.45	5.54	0.983 (0.876, 1.102)
T_{max} (h)[c]	1.0 (0.5, 1.5)	1.0 (0.5, 2.0)	N/A[d]

AUC=area under the plasma concentration-versus-time curve from time 0 to the last measurable concentration (AUC_{0-t}) and from time 0 to infinity ($AUC_{0-\infty}$); CI=confidence interval; C_{max}=maximum measured plasma concentration; N/A=not applicable; T_{max}=time to C_{max}
[a] Least squares geometric mean ratio
[b] Geometric mean
[c] Median (minimum, maximum)
[d] Ranked values of T_{max} were analyzed with the analysis of variance model (p=0.142)
Note: Tablet III formulation was used in this study.
Source: Study 1263-109 CSR, Table 10.2.5.1, Table 10.2.5.2, Table 10.2.5.4 and Table 8.

Figure 13. Mean Plasma Maribavir Concentrations After Single Oral Administration of Maribavir 100 mg Whole Tablet III Without and With Antacid, Study 1263-109



Source Study 1263-109 CSR, Table 10.2.1.2 and Table 10.2.1.3

Table 94. Statistical Analysis of the Pharmacokinetic Parameters of Maribavir Following a Single Oral Dose of Maribavir 100 mg Whole Tablet III Without and With Antacid, Study 1263-109

Parameter	Whole Tablet III + Antacid (N=15)	Whole Tablet III (N=15)	Whole Tablet III + Antacid/ Whole Tablet III[a] (90% CI) (N=15)
AUC_{0-t} (µg*h/mL)[b]	19.4	22.1	0.880 (0.818, 0.945)
$AUC_{0-\infty}$ (µg*h/mL)[b]	21.7	24.3	0.891 (0.828, 0.958)
C_{max} (µg/mL)[b]	4.64	5.54	0.837 (0.747, 0.939)
T_{max} (h)[c]	1.5 (0.5, 4.0)	1.0 (0.5, 2.0)	N/A[d]

AUC=area under the plasma concentration-versus-time curve from time 0 to the last measurable concentration (AUC_{0-t}) and from time 0 to infinity ($AUC_{0-\infty}$); CI=confidence interval; C_{max}=maximum measured plasma concentration; N/A=not applicable; T_{max}=time to C_{max}
[a] Least squares geometric mean ratio
[b] Geometric mean
[c] Median (minimum, maximum)
[d] Ranked values of T_{max} were analyzed with the analysis of variance model (p=0.142)
Note: Tablet III formulation was used in this study.
Source: Study 1263-109 CSR, Table 10.2.5.2, Table 10.2.5.3, Table 10.2.5.4, and Table 10.

Renal Impairment

In Study 1263-101, the PK of maribavir was evaluated in the fasted state after a single 400 mg dose in the following groups:

- Mild renal impairment: creatinine clearance (CLcr) 50 to 80 mL/min
- Moderate renal impairment: CLcr 30 to <50 mL/min
- Severe renal impairment: CLcr <30 mL/min
- Normal renal function: CLcr >80 mL/min

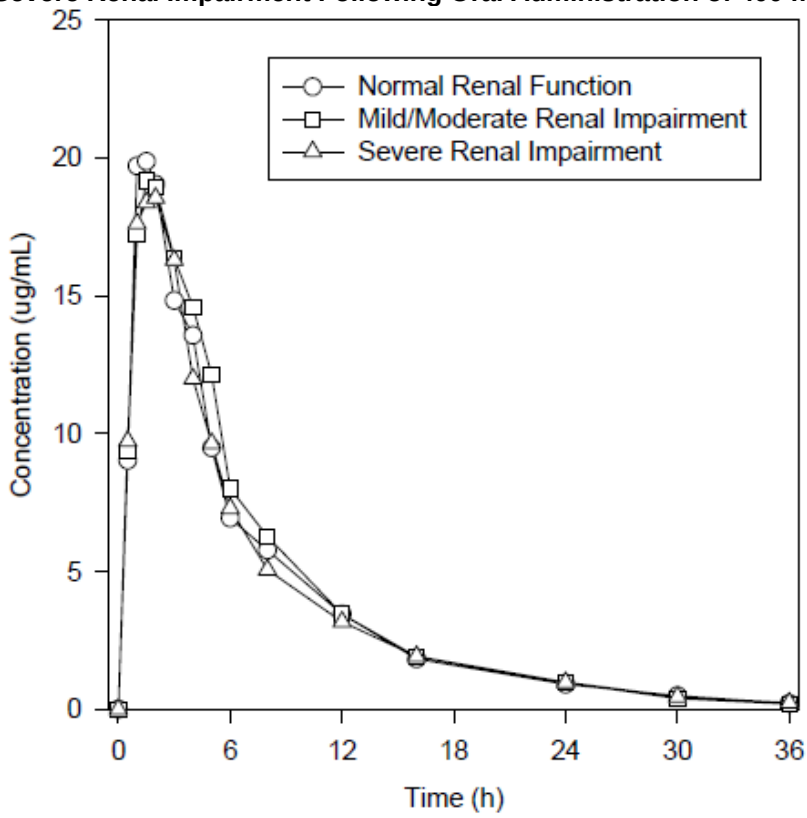
Blood and urine samples were collected through 36 hours postdose for measurement of maribavir and VP 44469 concentrations. Protein binding was measured using equilibrium dialysis in pre-dose, 2 hour and 12 hour postdose samples.

In subjects with renal impairment versus healthy controls, geometric mean ratios of maribavir total or unbound exposures ranged from 0.93 to 1.23 and geometric mean ratios of total VP 44469 ranged from 1.36 to 2.08.

The mean protein binding was >98% in all renal function categories.

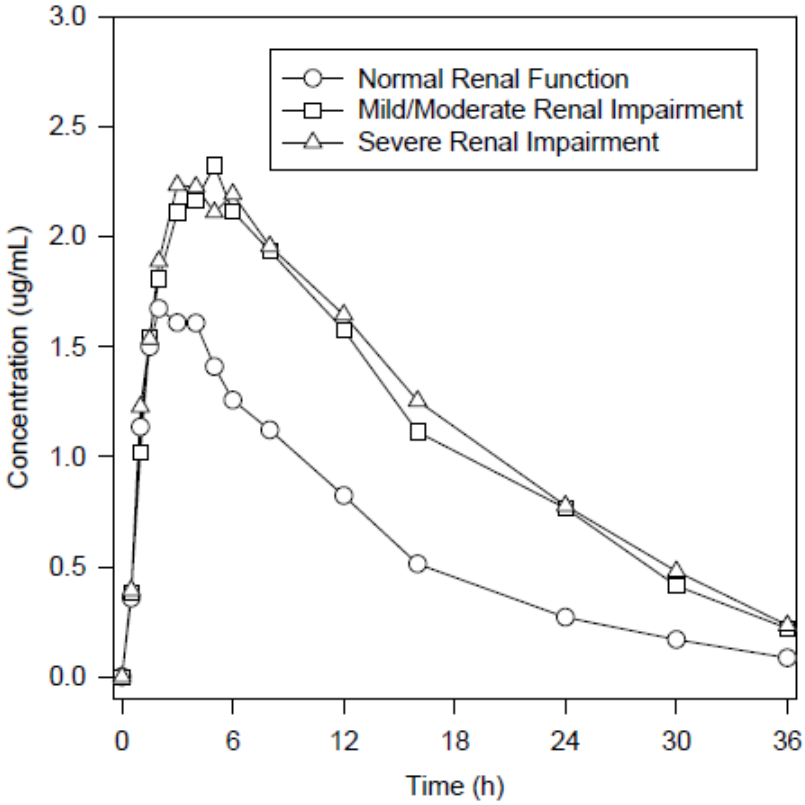
See Figure 14 and Figure 15, and Table 95.

Figure 14. Mean Plasma Maribavir Concentrations for Subjects With No, Mild/Moderate, and Severe Renal Impairment Following Oral Administration of 400 mg Maribavir



Source: Study report.

Figure 15. Mean Plasma VP 44469 Concentrations for Subjects With No, Mild/Moderate, Severe Renal Impairment Following Oral Administration of 400 mg Maribavir



Source: Study report.

Table 95. Statistical Analysis of the Pharmacokinetic Parameters of Maribavir and VP 44469 for Subjects With Mild/Moderate or Severe Renal Impairment Versus Healthy Control Subjects, Study 1263-101

Maribavir			
	Mild/Moderate Renal Impairment[a] N =10	**Healthy Control[a] N =12**	**Mild/Moderate Renal Impairment/Healthy Control[b] (90% CI) N =10**
$AUC_{0-\infty}$ (µg*h/mL)	138.3	127.6	1.084 (0.806, 1.458)
$AUC_{0-\infty,u}$ (µg*h/mL)	1.62	1.45	1.111 (0.817, 1.510)
C_{max} (µg/mL)	20.98	21.88	0.959 (0.767, 1.200)
$C_{max,u}$ (µg/mL)	0.246	0.236	1.043 (0.764, 1.425)
T_{max} (h)	1.8 (1.0, 4.0)	1.5 (1.0, 3.0)	NA
	Severe Renal Impairment[a] N = 8	**Healthy Control[a] N =12**	**Severe Renal Impairment/Healthy Control[b] (90% CI) N =8**
$AUC_{0-\infty}$ (µg*h/mL)	122.6	127.6	0.961 (0.701, 1.318)
$AUC_{0-\infty,u}$ (µg*h/mL)	1.74	1.45	1.197 (0.872, 1.643)
C_{max} (µg/mL)	20.34	21.88	0.930 (0.732, 1.180)
$C_{max,u}$ (µg/mL)	0.289	0.236	1.226 (0.888, 1.691)
T_{max} (h)	1.8 (1.0, 3.0)	1.5 (1.0, 3.0)	NA
VP 44469			
	Mild/Moderate Renal Impairment[a] N = 10	**Healthy Control[a] N = 12**	**Mild/Moderate Renal Impairment/Healthy Control[b] (90% CI) N = 10**
$AUC_{0-\infty}$ (µg*h/mL)	41.0	21.8	1.883 (1.511, 2.346)
C_{max} (µg/mL)	2.38	1.75	1.365 (1.091, 1.707)
T_{max} (h)	5.0 (2.0, 6.0)	3.0 (1.5, 6.0)	NA
	Severe Renal Impairment[a] N = 8	**Healthy Control[a] (90% CI) N = 12**	**Severe Renal Impairment/Healthy Control[b] (90% CI) N = 8**
$AUC_{0-\infty}$ (µg*h/mL)	45.4	21.8	2.084 (1.649, 2.635)
C_{max} (µg/mL)	2.37	1.75	1.355 (1.067, 1.720)
T_{max} (h)	4.5 (2.0, 8.0)	3.0 (1.5, 6.0)	NA

$AUC_{0-\infty}$=area under the plasma concentration vs time curve from time 0 to infinity; CI=confidence interval; C_{max}=maximum observed plasma drug concentration; NA=not applicable; T_{max}=time of maximum plasma drug concentration
[a] Geometric mean except T_{max}, which is presented as median (min, max).
[b] Least squares geometric mean ratio.
Source: Study 1263-101 CSR Amendment 1 - 06-Jul-2006 Section 10, Table 10.2.5.1, Table 10.2.5.2, Table 10.2.5.3, Table 10.2.5.6, Table 10.2.6.1, Table 10.2.6.2, Table 10.2.6.3, Table 10.2.6.6

Hepatic Impairment

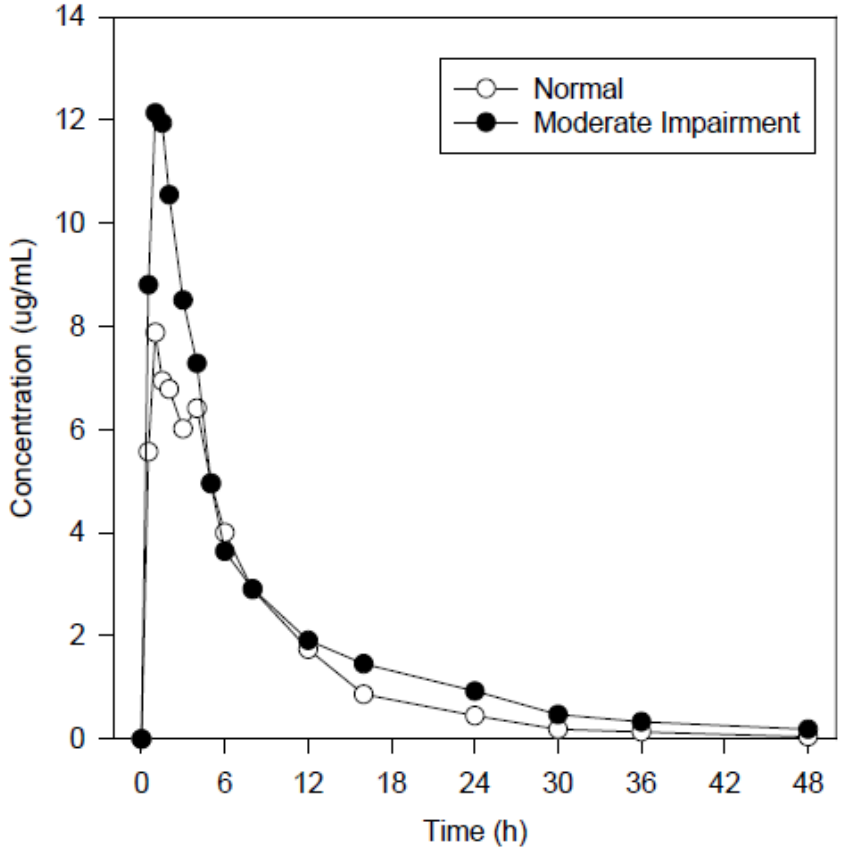
In Study 1263-103, the PK of maribavir was evaluated in the fasted state after a single 200 mg dose in 10 subjects with moderate hepatic impairment (Child-Pugh Class B [score of 7 to 9]) and 10 matched controls.

Blood samples were collected through 48 hours postdose for measurement of maribavir and VP 44469 concentrations. Protein binding was measured using equilibrium dialysis in predose, 2 hour and 12 hour postdose samples.

In subjects with moderate hepatic impairment versus healthy controls, geometric mean ratios of maribavir total or unbound exposures ranged from 1.03 to 1.35 and geometric mean ratios of total VP 44469 ranged from 1.19 to 1.31.

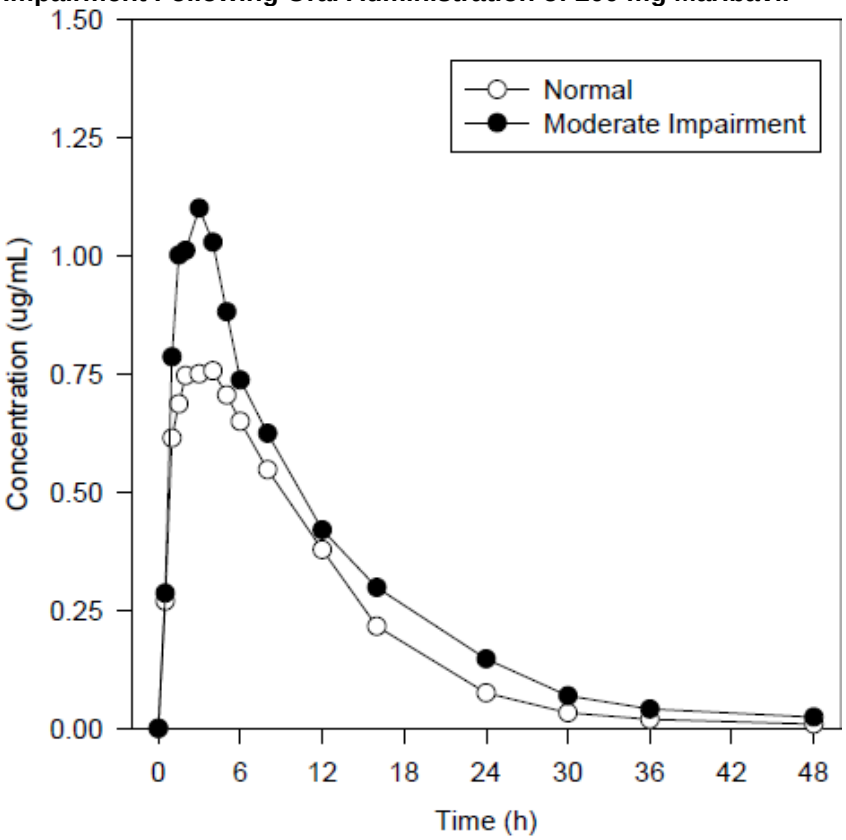
The mean protein binding was >98% in subjects with moderate hepatic impairment and controls. See Figure 16 and Figure 17, and Table 96.

Figure 16. Mean Plasma Maribavir Concentrations for Subjects With No and Moderate Hepatic Impairment Following Oral Administration of 200 mg Maribavir



Source: Study report.

Figure 17. Mean Plasma VP 44469 Concentrations for Subjects With No and Moderate Hepatic Impairment Following Oral Administration of 200 mg Maribavir



Source: Study report.

Table 96. Statistical Analysis of the Pharmacokinetic Parameters of Maribavir and VP 44469 for Subjects With Moderate Hepatic Impairment Versus Healthy Control Subjects, Study 1263-103

Maribavir			
	Moderate Hepatic Impairment[a] N =10	Healthy Control[a] Geometric Means N =10	Moderate Hepatic Impairment/Healthy Control[b] (90% CI) N =10
$AUC_{0-\infty}$ (µg*h/mL)	78.6	62.3	1.261 (0.889, 1.787)
$AUC_{0-\infty,u}$ (µg*h/mL)	0.946	0.918	1.030 (0.727, 1.460)
C_{max} (µg/mL)	12.72	9.45	1.346 (1.091, 1.660)
$C_{max,u}$ (µg/mL)	0.153	0.139	1.101 (0.892, 1.360)
T_{max} (h)	1.25 (0.5, 2.0)	1.0 (1.0, 5.0)	NA
VP 44469			
	Moderate Hepatic Impairment[a] N = 10	Healthy Control[a] N =10	Moderate Hepatic Impairment[b] (90% CI) N = 8
$AUC_{0-\infty}$ (µg*h/mL)	12.49	9.54	1.309 (1.007, 1.702)
C_{max} (µg/mL)	1.011	0.851	1.190 (0.836, 1.693)
T_{max} (h)	2.0 (1.0, 5.0)	2.0 (1.0, 5.0)	NA

$AUC_{0-\infty}$=area under the plasma concentration vs time curve from time 0 to infinity; $AUC_{0-\infty,u}$=unbound area under the plasma concentration vs time curve from time 0 to infinity; CI=confidence interval; C_{max}=maximum observed plasma drug concentration; $C_{max,u}$=maximum observed unbound plasma drug concentration; NA=not applicable; T_{max}=time of maximum plasma drug concentration;
[a] Geometric mean except T_{max}, which is presented as median (min, max).
[b] Least squares geometric mean ratio. Source: Study 1263-103 CSR Section 10, Table 10.2.5.1, Table 10.2.5.2, Table 10.2.5.4, Table 10.2.6.1, Table 10.2.6.2, Table 10.2.6.3, Table 10.2.6.4.

Effect of Ketoconazole on Maribavir

Study 1263-102 evaluated the PK of maribavir (CYP3A and P-glycoprotein [P-gp] substrate) in 19 healthy adults with and without ketoconazole (CYP3A and P-gp inhibitor) coadministration. All subjects received the following treatments in the fasted state separated by a 1-week washout:

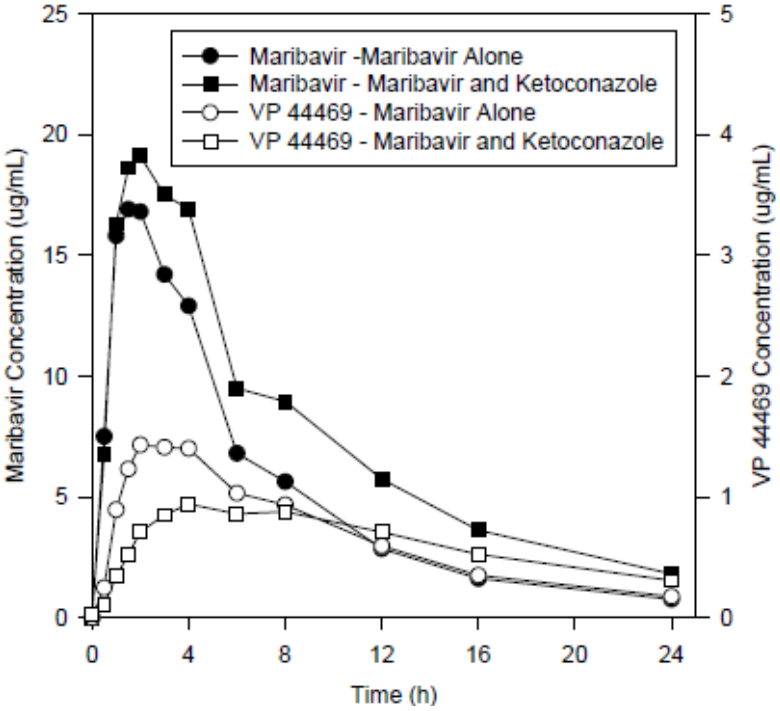
- Period 1: Single dose of maribavir 400 mg
- Period 2: Single dose of maribavir 400 mg 1 hour after a single dose of ketoconazole 400 mg

For measurement of maribavir and VP 44469 concentrations, the following samples were collected:

- Blood: collected through 16 hours postdose on Day 1 and Day 8 and 24 hours postdose on Day 2 and Day 9
- Urine: collected through 24 hours postdose on Day 1 and Day 8

In the presence versus absence of ketoconazole, geometric mean maribavir AUC was increased 53% and VP 44469 C_{max} decreased 40% (Figure 18 and Table 97).

Figure 18. Mean Plasma Maribavir and VP 44469 Concentration-Time Profiles Following Oral Administration of Maribavir Alone and Maribavir + Ketoconazole



Source: Study report.

Table 97. Statistical Analysis of the Pharmacokinetic Parameters of Maribavir and VP 44469 Following Coadministration of Ketoconazole, Study 1263-102

Parameter	Maribavir 400 mg + Ketoconazole[a] N=19	Maribavir 400 mg[a] N=19	Maribavir + Ketoconazole/ Maribavir (90% CI)[b] N=19
Maribavir			
$AUC_{0-\infty}$ (µg*h/mL)	183	119	1.533 (1.444, 1.628)
C_{max} (µg/mL)	21.3	19.4	1.097 (1.013, 1.188)
T_{max} (h)	1.5 (1.0, 4.0)	1.5 (1.0, 4.0)	NA
$t_{1/2}$ (h)	6.59	5.48	1.202 (1.131, 1.278)
CL/F (L/h)	2.2	3.4	0.652 (0.614, 0.693)
CLr (L/h)[c]	0.023	0.055	1.627 1.363, 1.944)
VP 44469			
$AUC_{0-\infty}$ (µg*h/mL)	19.7	17.1	1.153 (1.083, 1.228)
C_{max} (µg/mL)	0.9	1.6	0.598 (0.546, 0.656)
T_{max} (h)	4.0 (2.0, 12.0)	2.0 (1.0, 4.0)	NA
$t_{1/2}$ (h)	10.73	6.62	1.620 (1.429, 1.836)
CLr (L/h)[c]	5.963	6.601	0.912 (0.682, 1.219)

ANOVA=analysis of variance; $AUC_{0-\infty}$=area under the plasma concentration vs time curve from time 0 to infinity; CLr=renal clearance; CL/F=oral clearance; C_{max}=maximum observed plasma drug concentration; NA=not applicable; $t_{1/2}$=terminal half-life; T_{max}=time of maximum plasma drug concentration
[a] Geometric means except T_{max}, which is presented as median (min, max).
[b] Least squares geometric mean ratio and 90% confidence interval.
[c] CLr units were converted from mL/min to L/hr.
Source: Study 1263-102 CSR Section 10, Table 10.2.8.1, Table 10.2.8.2, Table 10.2.8.3, Table 10.2.9.1, Table 10.2.9.2, and Table 10.2.9.3

Effect of Rifampin on Maribavir

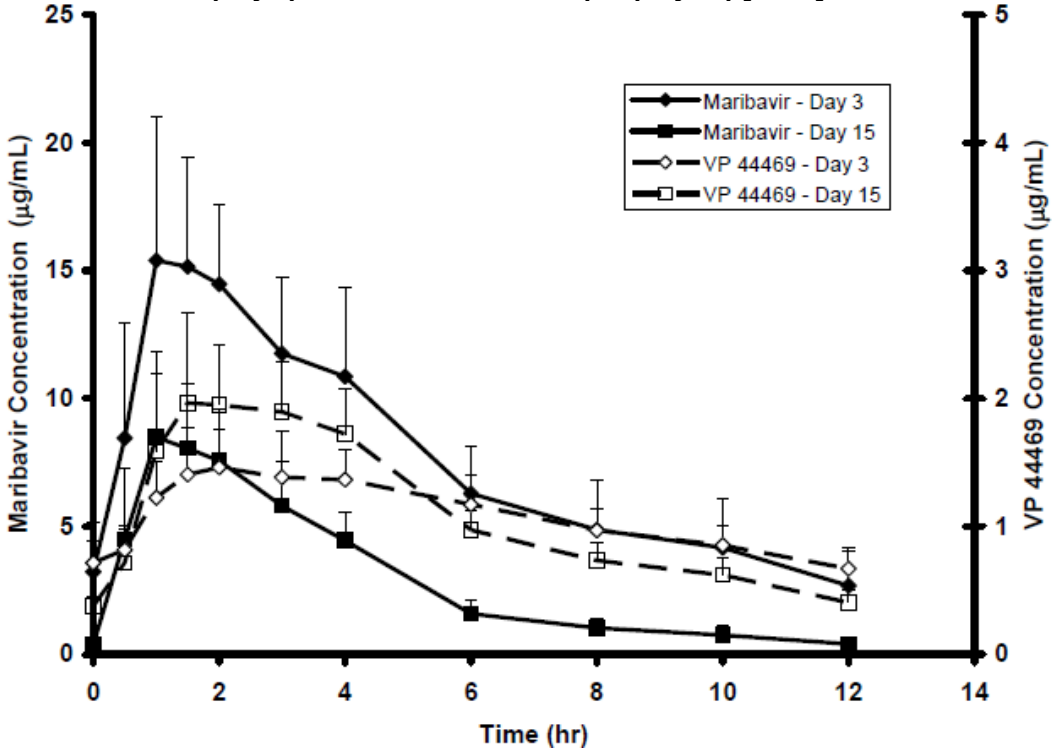
Study 1263-110 evaluated the PK of maribavir (CYP3A substrate) in 15 healthy adults with and without rifampin (strong CYP3A inducer) coadministration. Subjects received the following treatments (fasted state specified before the Day 3 and Day 15 doses):

- Day 1 to 2: Maribavir 400 mg BID
- Day 3: Maribavir 400 mg in the morning
- Day 4 to 12: Rifampin 600 mg once daily
- Day 13 to 14: Maribavir 400 mg BID and rifampin 600 mg once daily
- Day 15: Morning dose of maribavir and rifampin

Blood samples were collected through 12 hours postdose on Day 3 and Day 15 for measurement of maribavir and VP 44469 concentrations.

In the presence versus absence of ketoconazole, geometric mean maribavir AUC was decreased 60% and VP 44469 C_{max} increased 41% (Figure 19 and Table 98).

Figure 19. Mean Plasma Maribavir and VP 44469 Concentrations Following Oral Administration of Maribavir Alone (Day 3) and Maribavir + Rifampin (Day 15) [N=14]



Source: Study report.

Table 98. Statistical Analysis of the Pharmacokinetic Parameters of Maribavir and VP 44469 Following Coadministration of Rifampin, Study 1263-110

Maribavir			
	Maribavir + Rifampin[a] N =14	Maribavir[a] N =14	Maribavir + Rifampin /Maribavir[b] (90% CI) N =14
AUC_{0-t} (µg*h/mL)	34.5	86.6	0.398 (0.361, 0.440)
C_{max} (µg/mL)	9.88	16.2	0.612 (0.523, 0.717)
C_{trough} (µg/mL)	0.41	2.24	0.183 (0.135, 0.247)
T_{max} (h)	1.0 (1.0, 3.0)	1.3 (1.0, 4.0)	NA
$t_{1/2}$ (h)	2.67	3.79	0.704 (0.603, 0.822)
CL/F (L/h)[c]	11.6	4.62	2.505 (2.269, 2.766)
VP 44469			
	Maribavir + Rifampin[a] N =14	Maribavir[a] N =14	Maribavir + Rifampin /Maribavir[b] (90% CI) N =14
AUC_{0-t} (µg*h/mL)	12.9	12.9	1.004 (0.964, 1.046)
C_{max} (µg/mL)	2.13	1.51	1.412 (1.309, 1.522)
C_{trough} (µg/mL)	0.40	0.65	0.612 (0.535, 0.700)
T_{max} (h)	1.8 (1.0, 3.0)	2.0 (1.5, 4.0)	NA
$t_{1/2}$ (h)	4.66	7.23	0.644 (0.526, 0.788)

AUC_{0-t}= area under the plasma concentration vs time curve from time 0 to the last measurable concentration; $AUC_{0-\infty}$=area under the plasma concentration vs time curve from time 0 to infinity; CL/F=oral clearance; C_{max}=maximum observed plasma drug concentration; C_{trough}=observed plasma concentration at the end of a dosing interval; NA=not applicable; $t_{1/2}$=terminal half-life; T_{max}=time of maximum plasma drug concentration V_z/F=oral distribution volume
[a] Geometric mean except T_{max}, which is presented as median (min, max).
[b] Least squares geometric mean ratio and 90% confidence interval.
[c] CL units were converted from mL/min reported in the CSR to L/hr.
Source: Study 1263-110 CSR Section 10, Table 10.2.5.1, Table 10.2.5.2, Table 10.2.5.4, Table 10.2.6.1, Table 10.2.6.2, Table 10.2.6.4; Study C1263-110 CSR Addendum 1, Table 10.A.1, Table 10.A.2, Table 10.A.3, Table 10.A.4, Table 10.A.5, Table 10.A.6

Effect of Maribavir on CYP Substrates

Study 1263-100 evaluated the PK of CYP substrates with and without maribavir (in vitro inhibitor of CYPs 1A2, 2C9, 2C19, and 3A4) in 20 healthy adults. The following treatments were administered:

- Day -4: oral cocktail containing caffeine 2 mg/kg, warfarin 10 mg, vitamin K 10 mg, omeprazole 40 mg, and dextromethorphan 30 mg; intravenous midazolam 0.025 mg/kg
- Day 1 to 10: maribavir 400 mg BID
- Day 7: same cocktail administered on Day -4 coadministered with the morning maribavir dose

PK sampling times are summarized in Table 99.

Table 99. Summary of PK Sampling Times, Study 1263-100

Matrix	Analyte	CYP Substrate	Day	Duration of Sampling (Hours Postdose)
Blood	Warfarin	CYP2C9	Day -4-1 Day 7-11	92
Blood	Omeprazole 5-hydroxyomeprazole	CYP2C19	Day -4 and 7	2
Blood	Midazolam 1-hydroxymidazolam	CYP3A4	Day -4 and 7	8
Blood	Maribavir and VP 44469	Not applicable	Day -4 and 7	12
Urine	Caffeine metabolites Dextromethorphan Dextrorphan	CYP1A2 CYP2D6	Day -4 and 7	12

Source: Study report.
Abbreviations: CYP, cytochrome P450; PK, pharmacokinetics

In the presence versus absence of maribavir, geometric mean PK parameter ratios and 90% confidence intervals (CIs) were within bioequivalence limits (0.8 to 1.25) for caffeine metabolites, warfarin, and midazolam. Omeprazole geometric mean (90% CI) plasma concentration ratio was 1.71 (1.51, 1.92) and dextromethorphan/dextrorphan urinary concentration ratio was 1.18 (0.95, 1.41).

Effect of Maribavir on Voriconazole

Study 1263-107 evaluated the PK of voriconazole (CYP2C19 substrate) with and without maribavir (in vitro CYP2C19 inhibitor) in 19 healthy adults. Subjects received the following treatments (fasted state specified for the night before the Day -1 and Day 7 doses):

- Day -5: Voriconazole 400 mg BID
- Day -4 to 6: Voriconazole 200 mg BID
- Day 1 to 6: Maribavir 400 mg BID at the same time as voriconazole
- Day 7: Morning dose of voriconazole and maribavir

Blood samples were collected through 12 hours postdose on Days -1 and 7 for measurement of voriconazole and voriconazole-N-oxide concentrations.

In the presence versus absence of maribavir, voriconazole and metabolite geometric mean PK parameter ratios and 90% CIs were within bioequivalence limits (0.8 to 1.25).

Effect of Maribavir on Digoxin and Dextromethorphan

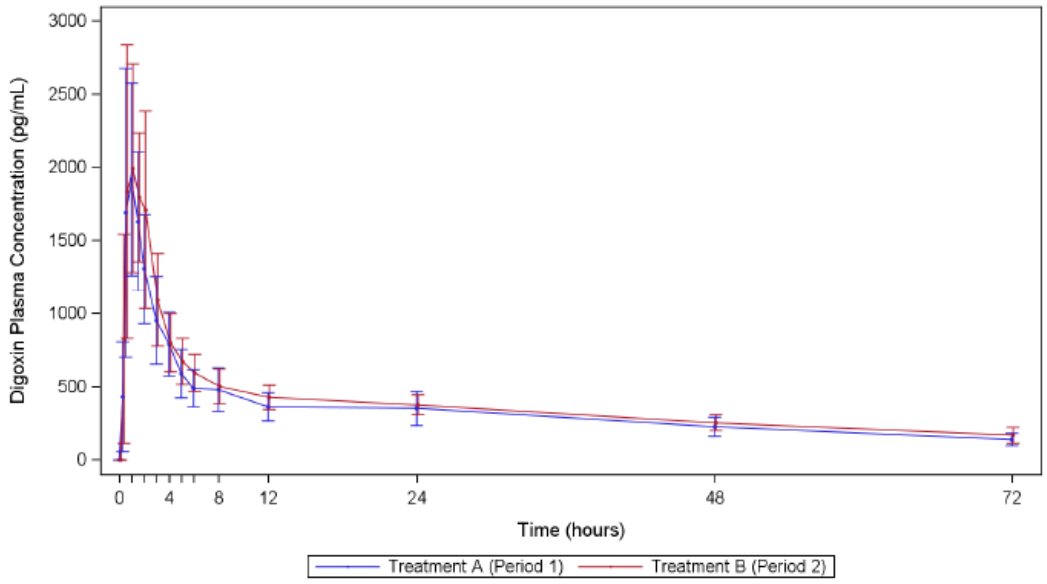
Study SHP620-115 evaluated the effect of maribavir (in vitro P-gp inhibitor, not an in vitro CYP2D6 substrate) on the PK of digoxin (P-gp substrate) and dextromethorphan (CYP2D6 substrate) in 18 healthy adults. Subjects received the following treatments (fasted state specified for the night before the Day 1 and Day 13 doses):

- Day 1: Digoxin 0.5 mg and dextromethorphan 30 mg orally (Period 1)
- Day 8 to 15: Maribavir 400 mg BID orally
- Day 13: Digoxin 0.5 mg and dextromethorphan 30 mg orally with the morning dose of maribavir (Period 2)

Blood samples were collected through 72 hours postdose on Days 1 to 4 and 13 to 16 for measurement of digoxin, dextromethorphan and dextrorphan concentrations and through 12 hours postdose on Day 13 for measurement of maribavir.

In the presence versus absence of maribavir, geometric mean digoxin C_{max} was increased 25%, though this was not apparent graphically (Figure 20, Table 100). Dextromethorphan exposures were unchanged; either not statistically significant (dextromethorphan) or within bioequivalence limits (dextrorphan) (Table 101).

Figure 20. Mean Plasma Concentration-Time Profile for Digoxin by Treatment



Notes: Treatment A: Digoxin 0.5 mg + dextromethorphan 30 mg.
Treatment B: Maribavir 400 mg + digoxin 0.5 mg + dextromethorphan 30 mg.
Source: Study report.

Table 100. Statistical Analysis for PK Parameters of Digoxin Following Coadministration of Maribavir, Study SHP620-115

Parameter	Digoxin + Maribavir[a] (N=17)	Digoxin[a] (N=18)	Digoxin + Maribavir/ Digoxin[b] (90% CI)
$AUC_{0-\infty}$ (ng*h/mL)	38.1	31.6	1.206 (1.099, 1.324)
C_{max} (ng/mL)	2.42	1.94	1.248 (1.130, 1.378)
T_{max} (h)	1.0 (0.5, 2.0)	1.0 (0.5, 1.5)	NA

$AUC_{0-\infty}$=area under the curve extrapolated to infinity, calculated using the observed value of the last nonzero concentration;; CI=confidence interval; C_{max}=maximum observed concentration; CV=coefficient of variation, T_{max}=time to maximum observed plasma concentration
Digoxin treatment=digoxin 0.5 mg + dextromethorphan 30 mg; Digoxin + maribavir=maribavir 400 mg + digoxin 0.5 mg + dextromethorphan 30 mg.
[a] Geometric mean except T_{max}, which is presented as median (min, max).
[b] Least squares geometric mean ratios.
Source: Study SHP620-115 CSR, Table 15, and Table 16

Table 101. Summary of Pharmacokinetic Parameters for Dextromethorphan and Dextromethorphan/Dextrorphan (Parent Versus Metabolite) Ratio by Treatment (Pharmacokinetic Set), Study SHP620-115

	Dextromethorphan + Maribavir [a] N=18	Dextromethorphan [a] N=17	Dextromethorphan /Dextrorphan [b] (90% CI) N=17
Dextromethorphan			
AUC_{0-t} (ng*h/mL)	6.77	7.06	0.882 (0.696, 1.118)
C_{max} (ng/mL)	1.14	1.14	0.944 (0.778, 1.144)
T_{max} (h)	3.0 (2.0-5.0)	3.0 (1.5-5.0)	NA
Dextrorphan			
AUC_{0-t} (ng*h/mL)	2110	2200	0.973 (0.949, 0.998)
$AUC_{0-\infty}$ (ng*h/mL)	2150	2270	0.971 (0.943, 0.999)
C_{max} (ng/mL)	401	433	0.943 (0.883, 1.007)
T_{max} (h)	2.0 (1.0-4.0)	2.0 (1.5-3.0)	NA
Dextromethorphan/Dextrorphan			
AUC_{0-t} ratio	0.003	0.003	0.905 (0.721, 1.138)

AUC_{0-t}=area under the curve from the time of dosing to the last measurable concentration; CI=confidence interval; C_{max}=maximum observed concentration; CV=coefficient of variation; T_{max}=time of maximum observed concentration sampled during a dosing interval
[a] All values presented as geometric mean except T_{max}, which are presented as median (min, max)
[b] Least squares geometric mean ratios.
Source: Study SHP620-115 CSR, Table 18, Table 19, Table 20

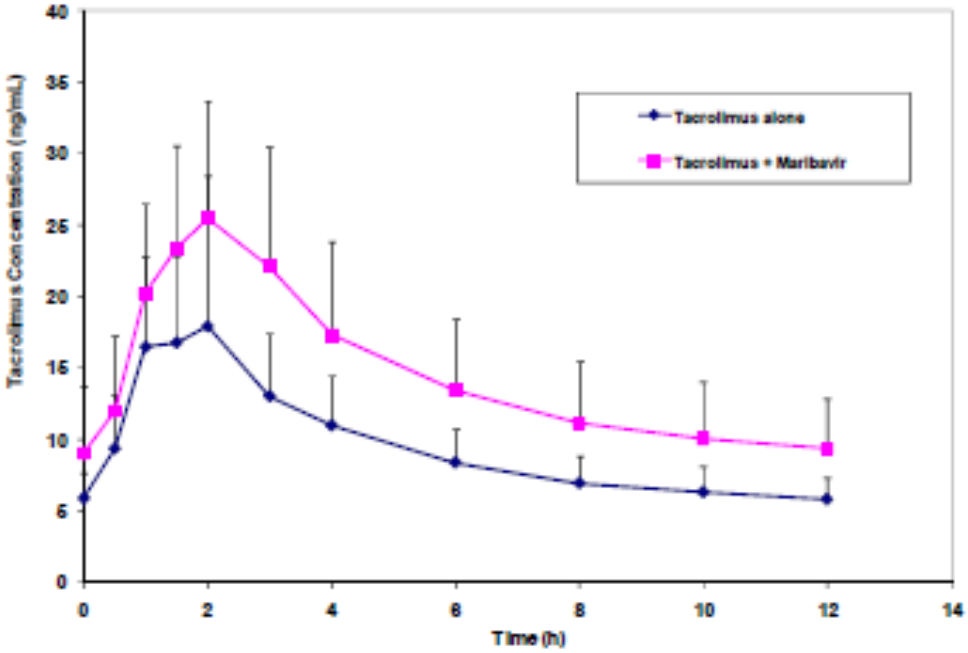
Effect of Maribavir on Tacrolimus

Study 1263-105 evaluated the PK of maribavir (in vitro CYP3A4 inhibitor) on the PK of tacrolimus (CYP3A4 substrate) in 24 renal transplant recipients on stable tacrolimus therapy. Subjects received tacrolimus doses in the clinic on PK sampling days (Day -1 and 7). Maribavir 400 mg BID was coadministered with tacrolimus on Day -1 through the morning dose on Day 7. Fasted administration was specified for Days -1 and 7.

Blood samples were collected through 12 hours postdose on Day -1 for measurement of tacrolimus and on Day 7 for measurement of tacrolimus and maribavir.

In the presence versus absence of maribavir, geometric mean (90% CI) tacrolimus ratios were 1.57 (1.41, 1.74) (Table 102 and Figure 21).

Figure 21. Mean Whole Blood Tacrolimus Concentrations in Renal Transplant Recipients on Tacrolimus Treatment Alone (Day -1) and in Combination With Maribavir (Day 7)



Source: Study report.
Vertical bars represent standard deviation.

Table 102. Statistical Analysis of the Pharmacokinetic Parameters of Tacrolimus With and Without Maribavir Coadministration, Study 1263-105

Parameter	Tacrolimus + Maribavir[a] N=16	Tacrolimus[a] N=20	Tacrolimus + Maribavir/ Tacrolimus[b] (90% CI)
AUC_{0-t} (ng*h/mL)	166	110	1.511 (1.386, 1.648)
C_{max} (ng/mL)	26.1	19.0	1.376 (1.202, 1.574)
C_{trough} (ng/mL)	8.82	5.64	1.566 (1.409, 1.740)
T_{max} (h)	2.0 (1.0, 3.0)	1.5 (0.5, 3.0)	NA

AUC_{0-t}= area under the plasma concentration vs time curve from time 0 to the last measurable concentration; C_{max}=maximum observed plasma drug concentration; C_{trough}=observed plasma concentration at the end of a dosing interval; NA=not applicable; T_{max}=time of maximum plasma drug concentration
[a] Geometric means except T_{max}, which is presented as median (min, max).
[b] Least squares geometric mean ratios.
Source: Study 1263-105 CSR Section 10, Table 10.2.5.3, Table 10.2.5.5, Table 10.2.8.1, Table 10.2.9.2, Table 10.2.11.2

Effect of Maribavir on the QTc Interval

Study 1263-108 was a single dose, 4-period crossover study in 50 healthy adults to evaluate the effect of maribavir on the corrected QT interval (QTc). Subjects received the following treatments in the fasted state and with a 4- to 14-day washout period between treatments: placebo (Treatment A), maribavir 100 mg (Treatment B, therapeutic dose), maribavir 1,200 mg (Treatment C, supratherapeutic dose), or moxifloxacin 400 mg (positive control).

Blood samples were collected through 22 hours postdose for measurement of maribavir and VP 44469 concentrations. Continuous electrocardiogram measurements were conducted through 22 hours postdose in each period.

No significant QT interval prolongation effect of maribavir (100 mg and 1,200 mg) was detected.

The largest upper bounds of the two-sided 90% CI for the mean difference between maribavir (100 mg and 1,200 mg) and placebo were below 10 milliseconds, the threshold for regulatory concern as described in ICH E14 guidance (investigational new drug application 51001, QT interval Interdisciplinary Review Team review dated September 11, 2009).

14.3. Bioanalytical Methods

Bioanalytical methods used to measure maribavir in human plasma were fully validated and met precision and accuracy acceptance criteria (±15%, ±20% at the lower limit of quantification) (Table 103). Method A7177M-SHP620 supported Phase 3 Study 303.

Table 103. Bioanalytical Methods Used to Quantify Maribavir in Plasma

Method Number	Analytical Technique	Calibration Range (ng/mL)	Long-Term Stability	Supported Clinical Studies
A11970M-SHP620	HPLC	51 to 5,105	1 month at -20°C	CMAB1001
A11972M-SHP620	HPLC	50 to 8000	3.5 months at -20°C	CMAA1003
A11981M-SHP620	LC-MS/MS	5 to 1,000	41 days at -20°C 253 days at -70°C	1263-105 1263-106
A11980M-SHP620	LC-MS/MS	5 to 1,000	293 days at -70°C	1263-102 1263-103 1263-104
A11982M-SHP620	LC-MS/MS	200-40,000	355 days at -20°C 260 days at -70°C	1263-108 1263-109 1263-110
A11978M-SHP620	LC-MS/MS	5 to 1,000	4 days at -20°C 370 days at -80°C	1263-100 1263-101
A7177M-SHP620	LC-MS/MS	200 to 100,000	2067 days at -20°C 779 days at -80°C	SHP620-115 SHP620-303
A11985M-SHP620	LC-MS/MS	200 to 100,000	355 days at -20°C	SHP620-202

Source: Biopharmaceutics Summary.
Abbreviations: HPLC, high-performance liquid chromatography; LC-MS/MS, liquid chromatography-tandem mass spectrometry

14.4. Pharmacometrics Assessment

Review Summary

Applicant's population pharmacokinetics (PopPK) model is acceptable to derive individual predicted exposure metrics (steady-state AUC and C_{max}) for exposure-response analyses and support the labeling language with regards to intrinsic factors (age, weight, sex, race, and ethnicity). Parameters were estimated with acceptable precisions and ETA shrinkages are low for CL (6.1%) and moderate (<40%) for other parameters. There is no unacceptable bias in goodness-of-fit plots and the prediction corrected visual predictive check plots generally captures the central tendency and variability of the observed concentrations. In the Applicant's exposure-response analyses for efficacy based on the data from Phase 3 study (Trial 303), no positive exposure-response relationship was observed for CMV viremia clearance at Week 8 at the maribavir exposures at the proposed dose of 400 mg BID.

14.4.1. Applicant's Population PK Analysis

Title

Population Pharmacokinetic Analysis of Maribavir in Adult Healthy Subjects and Transplant Recipients with CMV Infection or Diseases

Objectives

To develop an adult PopPK model for maribavir using PK data from nine Phase 1 studies, Phase 2 Studies, SHP620-202 (Trial 2 202) and SHP620-203 (Trial 2 203), and a Phase 3 Study, SHP620-303 (Trial 303) to support the regulatory filing of maribavir

Analysis Data

The PopPK analysis included data from nine Phase 1 studies (1263-101, 1263-102, 1263-103, 1263-104, 1263-109, 1263-100, 1263-105, 1263-110 and SHP620-115), two Phase 2 studies (Studies 202 and 203) and a Phase 3 Study (Trial 303). Of the 5,950 quantifiable maribavir concentrations, 2,378 were from 485 transplant patients with CMV, 2,952 were from 133 healthy volunteers, 148 were from 10 subjects with mild or moderate hepatic impairment, 220 were from 20 stable renal transplant subjects and the remaining 252 were from 19 subjects with renal impairment of varying degree (mild, moderate, and severe).

The median (range) age was 53 (18 to 79) years with median (range) weight of 74 (36 to 141) kg. There were more male subjects (59%) than female subjects (41%). The majority of the subjects were Caucasian (77%). There were 17% black, 3% Asian and 4% other. Of the 667 subjects, 20% were healthy volunteers, 73% transplant patients with CMV, 3% subjects with renal impairment, 1% subjects with hepatic impairment and 3% stable renal transplant patients. For the demographic and baseline characteristics by study, refer to Applicant's PopPK Report, Table 5-2, page 52 to 57.

Base Model

The base PopPK model (Run 059) for maribavir was developed using the data from nine Phase 1 studies and the two Phase 2 studies. The structural model was a two-compartment disposition model with first-order absorption and elimination, and an absorption lag-time. Interindividual variability (IIV) was estimated on all parameters and a full variance covariance matrix was included. A proportional residual error model was used. The model included effects of CYP3A inhibitor and inducer on apparent clearance (CL/F) with power model. Weight effect was added on CL/F, apparent volume of distribution in the central compartment (Vc/F), apparent intercompartmental clearance (Q/F) and apparent volume of distribution in the peripheral compartment (Vp/F) with fixed allometric scalars (0.75 for clearances and 1 for volumes of distribution). Monte-Carlo importance sampling expectation maximization was the method of parameter estimation.

Covariate Analysis

In addition to body weight, strong CYP3A inhibitors and strong CYP3A inducers which were already included in the base model, the following covariates were evaluated by ETA-covariate

plots: age, body mass index (BMI), sex, race, ethnicity, health status, study, diarrhea, vomiting, dose, disease characteristics such as transplant type, baseline plasma CMV deoxyribonucleic acid (DNA), CMV category (asymptomatic CMV infection, CMV organ disease, and symptomatic CMV infection), hepatic impairment, presence of CMV substitutions, baseline use of antilymphocyte antibody, episode of qualifying infection, prior use of CMV prophylaxis, gastrointestinal graft-versus-host disease), concurrent medications of strong CYP3A inhibitors, concurrent medications of strong CYP3A inducers, concurrent medications of acid-reducing agents such as H2 blockers, proton pump inhibitors, and antacids.

The full model included sex on CL/F and Vc/F, dose on the dissociation constant (K_a) and Child-Pugh class B on Vc/F, in addition to the effect of weight, strong CYP3A inhibitors and strong CYP3A inducers. A backwards deletion approach identified that the effect of strong CYP3A inhibitors and strong CYP3A inducers on CL/F and dose on K_a are significant predictors of maribavir PK. Formulation was not evaluated as a covariate in the PopPK analysis as it was found not to affect maribavir PK significantly based on available data from individual Phase 1 studies and separate cross-study analyses of Phase 1 data.

Final Model

The final PK model (Run 171) was a two-compartment disposition model with first-order absorption and elimination, and an absorption lag-time. The model included CYP3A inhibitor and inducer effects on CL/F, dose effect on K_a and patient status (transplant with CMV) effect on CL/F. In addition, CL/F, Vc/F, Q/F, and Vp/F increased with weight fixed to allometric scalars. Parameter estimates of the final PK model are shown in Table 104. The standard goodness of plots and the prediction-corrected visual predictive check plots are presented in Figure 22 and Figure 23.

Table 104. Parameter Estimates of the Final PopPK Model

Parameter	Units	NONMEM Estimates				MCMC BAYES Estimates[a]
		Estimate[a]	%RSE[b]	95% CI[a]	IIV CV%[c] (%RSE)	Median [95% CI]
CL/F	L/hr	3.77	3.79	3.50 to 4.06	52.5 (6.43)	3.79 [3.54 to 4.10]
Vc/F	L	18.6	3.45	17.3 to 19.8	34.0 (14.4)	17.7 [16.5 to 19.1]
Q/F	L/hr	0.908	12.9	0.705 to 1.17	90.7 (24.5)	0.841 [0.692 to 1.04]
Vp/F	L	8.66	10.4	7.05 to 10.6	103 (20.7)	7.26 [6.08 to 8.85]
Ka	hr^{-1}	0.336	10.9	0.271 to 0.415	152 (14.2)	0.396 [0.299 to 0.521]
Lag-time	hr	0.271	5.91	0.241 to 0.304	44.1 (28.8)	0.253 [0.218 to 0.284]
CL/F~weight	unitless	0.75 fixed	-	-	-	0.75 fixed
Vc/F~weight	unitless	1 fixed	-	-	-	1 fixed
Q/F~weight	unitless	0.75 fixed	-	-	-	0.75 fixed
Vp/F~weight	unitless	1 fixed	-	-	-	1 fixed
CL/F~CYP3A strong inhibitors	unitless	0.700	1.98	0.673 to 0.727		0.704 [0.678 to 0.733]
CL/F~CYP3A strong inducers	unitless	2.24	2.95	2.11 to 2.37		2.23 [2.13 to 2.34]
Ka~dose	unitless	-1.94	6.49	-2.19 to -1.70		-1.78 [-2.08 to -1.49]
CL/F~ transplant patients with CMV	unitless	0.756	4.63	0.690 to 0.827		0.747 [0.684 to 0.817]
$\sigma^2_{prop\ Phase\ 1}$	unitless	0.0673	2.86	0.0635-0.0710	25.9[d]	0.0682 [0.0645 to 0.0723]
$\sigma^2_{prop\ Phase\ 2\ \&\ 3}$	unitless	0.137	3.67	0.127-0.147	37.0[d]	0.136 [0.127 to 0.147]

[a] Back-transformed from natural log scale (except for σ^2, CL/F~ weight, Vc/F~weight, Q/F~weight, Vp/F~weight, CL/F~CYP3A strong inhibitors, CL/F~CYP3A strong inducers, Ka~dose)

[b] RSE=SE.100 (except for σ^2, CL/F~ weight, Vc/F~weight, Q/F~weight, Vp/F~weight, CL/F~CYP3A strong inhibitors, CL/F~CYP3A strong inducers, Ka~dose). RSE for σ^2, CL/F~ weight, Vc/F~weight, Q/F~weight, Vp/F~weight, CL/F~CYP3A strong inhibitors, CL/F~CYP3A strong inducers, Ka~dose =SE(θ)/θ.100

[c] CV for IIV calculated as $CV_{TVP}=\sqrt{e^{\omega^2_P}}$ .100 if $\omega^2_P \leq 0.15$, else $CV_{TV_P}=\sqrt{e^{\omega^2_P}-1}$ .100

[d] Proportional residual error expressed as CV.

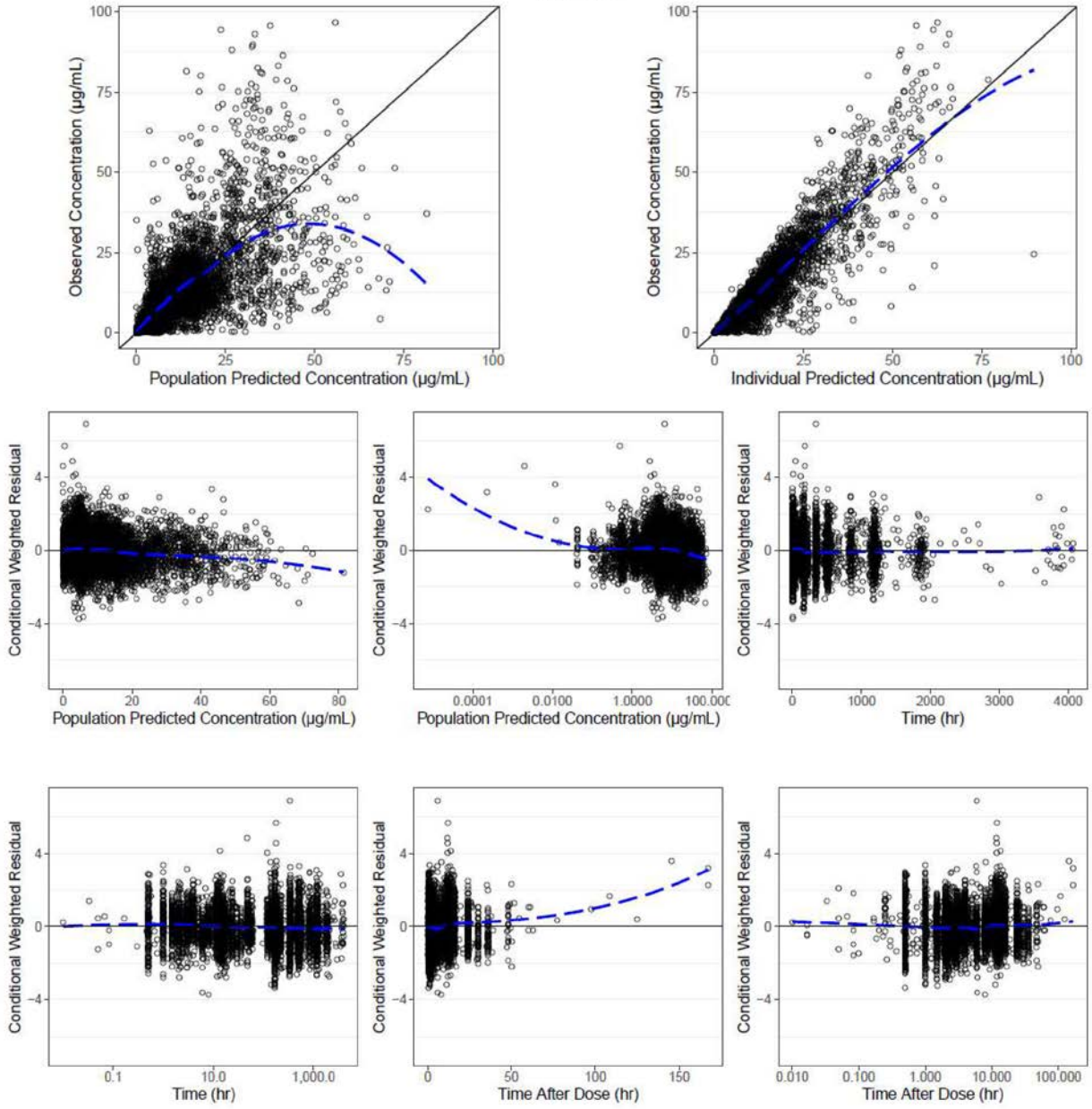
Source: Applicant's PopPK Report, Table 5-7; page 74.

The reference population is a 70 kg subject without CMV and administered 800 mg maribavir in the absence of CYP3A strong inh bitors or inducers.

Abbreviations: CI, confidence interval; CL/F, apparent clearance; CMV, cytomegalovirus; CYP, cytochrome P450; IIV, intraindividual variability; Ka, dissociation constant; MCMC, Markov chain Monte Carlo; NONMEM, nonlinear mixed effects modeling; Q/F, apparent intercompartmental clearance; RSE, relative standard error; Vc/F, apparent volume of distribution in the central compartment; Vp/F, apparent volume of distribution in the central compartment; Vp/F, apparent volume of distribution in the central compartment; Vp/F, apparent volume of distribution in the peripheral compartment

Reviewer's comments: The Applicant noted that % coefficient of variation for IIV was calculated by sqrt(exp(ω^2)), if ω^2 is less than 0.15. This appears to be typos, % coefficient of variation for IIV approximates sqrt(ω^2) at lower ω. As all ω^2 estimates for PK parameters (CL/F, Vc/F, Q/F, Vp/F, K_a, Lag-time) were greater than 0.15, this typo does not affect the IIV estimations.

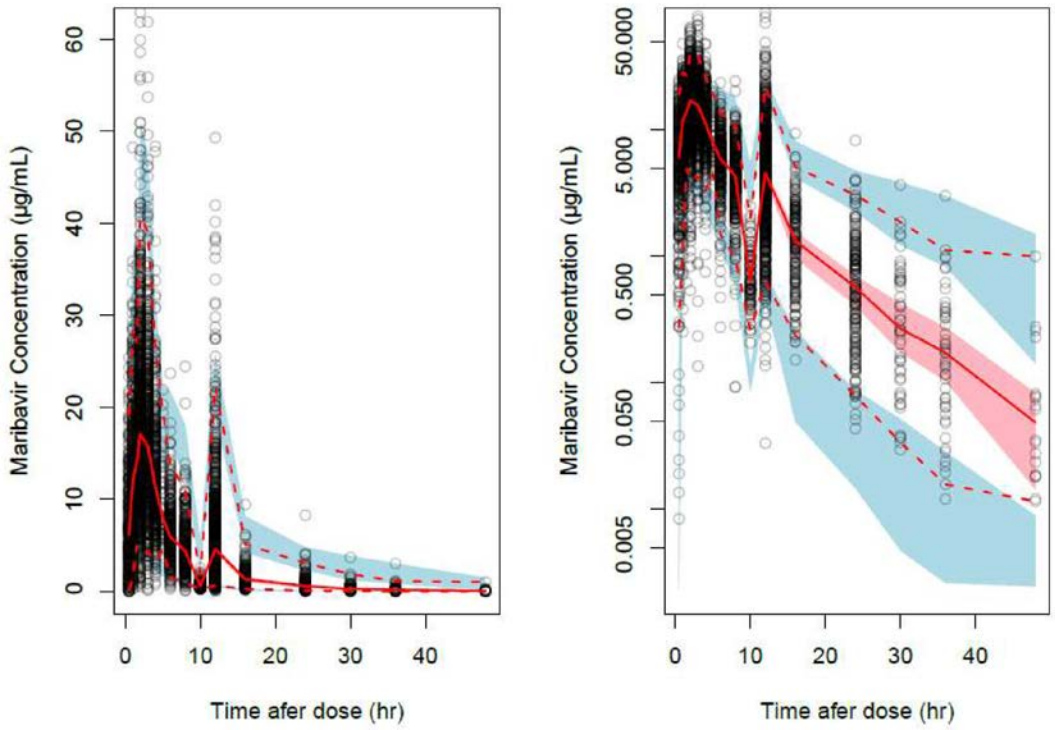
Figure 22. Goodness-of-Fit Plots for the Final Population Pharmacokinetics Model



Blue dashed line: Local regression (Loess) smoothing line

Source: Applicant's Population Pharmacokinetics Report, Figures 5-3 and 5-4; pages 76-77.

Figure 23. Prediction-Corrected Visual Predictive Check for the Final PopPK Model



Source: Applicant's PopPK Report, Figure 5-6; page 79.
Abbreviation: PopPK, population pharmacokinetics

First-order absorption rate constant decreased with increasing dose, estimated to be 1.29, 0.336 and 0.153 hr^{-1} following 400, 800 and 1,200 mg, respectively. Strong CYP3A inhibitors (used in 22% transplant patients with CMV) and strong CYP3A inducers (used in 1% transplant patients with CMV) were found to have a significant impact on maribavir PK with a 30% lower and a 2.24-fold higher clearance, respectively. Clearance was 24% lower for transplant patients with CMV compared to all other subjects. $AUC_{0-\tau}$ was 27% higher in transplant patients with CMV compared to healthy subjects, but steady-state C_{max} was comparable.

The Applicant noted that although body weight was not found to be a significant predictor of maribavir PK, it was retained in the model with fixed allometric coefficients for potential use of the PopPK model in a pediatric development program. The individual exposure estimates indicated that steady-state $AUC_{0-\tau}$ and C_{max} were 25% and 31% higher, in underweight (BMI <18.5 kg/m^2) patients compared to normal weight (18.5≤ BMI ≥25 kg/m^2) but comparable in overweight (25≤ BMI ≥30 kg/m^2) patients, and obese (BMI ≥30 kg/m^2) and normal weight patients.

There was no evidence that age, sex, race, ethnicity, study, diarrhea, vomiting, disease characteristics, moderate and weak CYP3A inhibitors, H_2 blockers, proton pump inhibitors, and antacids affected maribavir PK. There were insufficient number of subjects taking moderate (none) and weak (one subject) CYP3A inducers to evaluate their effect.

Reviewer's assessment: The final PopPK model is acceptable to describe time-concentration profiles of maribavir for healthy subjects and transplant patients with CMV infection following oral administration of maribavir. Parameters were estimated with acceptable precisions with %relative standard error <15% for fixed effects, and <30% for random effects. ETA shrinkages

are low for CL (6.1%) and moderate (<40%) for other parameters. Generally, there is no notable bias in goodness-of-fit plots and the prediction-corrected visual predictive check plots generally captures the central tendency and variability of the observed concentrations. This model is acceptable to derive individual predicted exposure metrics for exposure-response analysis.

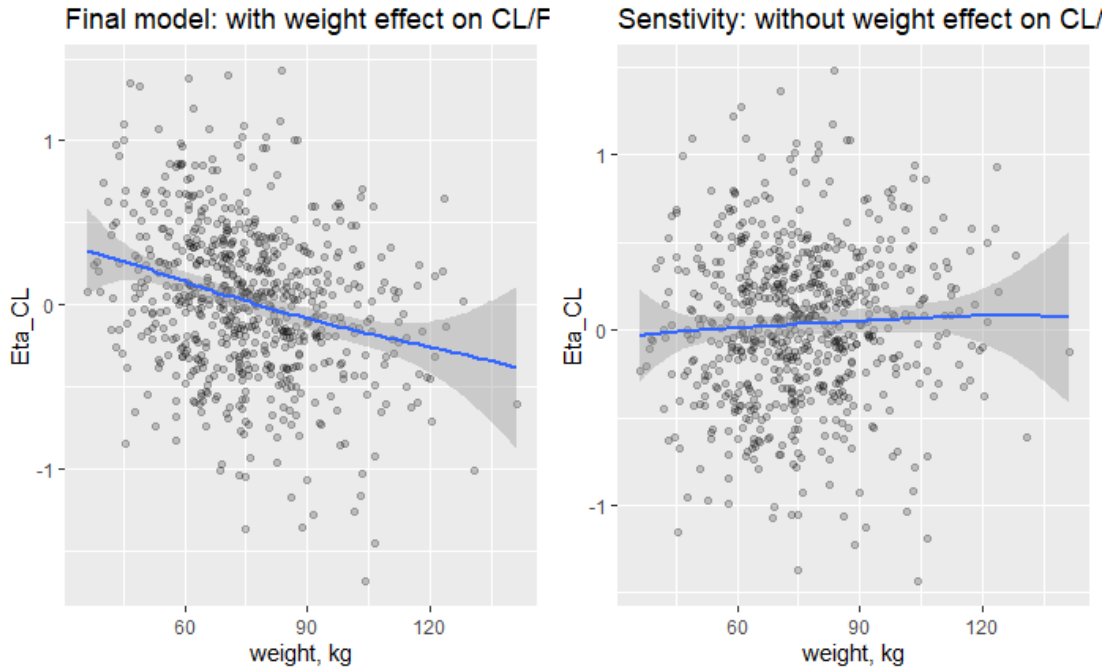
The model estimated covariate effects of strong CYP3A inhibitors/inducers are consistent with those observed in the drug-drug interaction (DDI) studies: in Study 1264-102, oral clearance of maribavir was 35% lower with coadministration of ketoconazole, and in Study 1263-110, oral clearance of maribavir increased 2.5-fold and $t_{1/2}$ decreased 30% with coadministration of rifampin.

The Applicant reported that body weight was not identified as a significant predictor in their model development, however, were retained in the final model. The reviewer notes that ETA-covariate plot shows a notable trend in the ETA for CL to weight relationships with the final model (including weight effect on CL/F) (left panel of Figure 24). In the reviewer's sensitivity analysis by removing weight-model from CL/F, the bias in ETA for CL-weight relationship was not observed, which further suggests that body weight does not significantly impact maribavir PK. Including effects of body size on maribavir PK with theoretical allometric scaling may be biologically plausible, especially when PopPK model is used for exploration of different dose in pediatric population as the Applicant noted. However, the weight effect on PK parameters should not be included in the model, when any simulations are performed for adult population, because biased CL/F values will be forced by the covariate model.

To derive individual predicted exposures for the exposure-response (E-R) analysis and summary statistics for maribavir exposures in the labelling, the current model is considered acceptable. The parameter estimates from the sensitivity analysis are similar to those from the final model except for Q/F. The individual predicted PK parameters (CL/F, Vc/F, Q/F, and Vp/F) from the sensitivity model were closely similar to those predicted from the Applicant's final model. Therefore, inclusion of body weight effect is not expected to affect the individual predicted exposures nor result in the different conclusions regarding covariate effects to support the labelling language.

ETA-covariates relationships with age, and sex did not show obvious trend. ETA for CL/F and Vc/F appears to be higher in Asian and Others compared to Caucasian, and black patient, however these observations are based on relatively small sample size (3% and 4% of PopPK analysis population). Individual prediction based on the final model did not show a clinical meaningful difference in maribavir exposure based on race (Caucasian, Black, Asian, and Others) and ethnicity (non-Hispanic or Hispanic).

Figure 24. ETA for CL/F—Body-Weight Relationships for Applicant's Final Model (Left) and the Reviewer's Sensitivity Model (Right)



Source: Reviewer's figure.
Left plot was generated by the Applicant's final model. Right plot was generated by the reviewer's sensitivity run.
Abbreviations: CL, clearance; CL/F, apparent clearance

14.4.2. Applicant's Exposure-Response Analyses

Exposure-Response Analysis for Efficacy: Phase 2 Studies (Trial 202 and Trial 203)

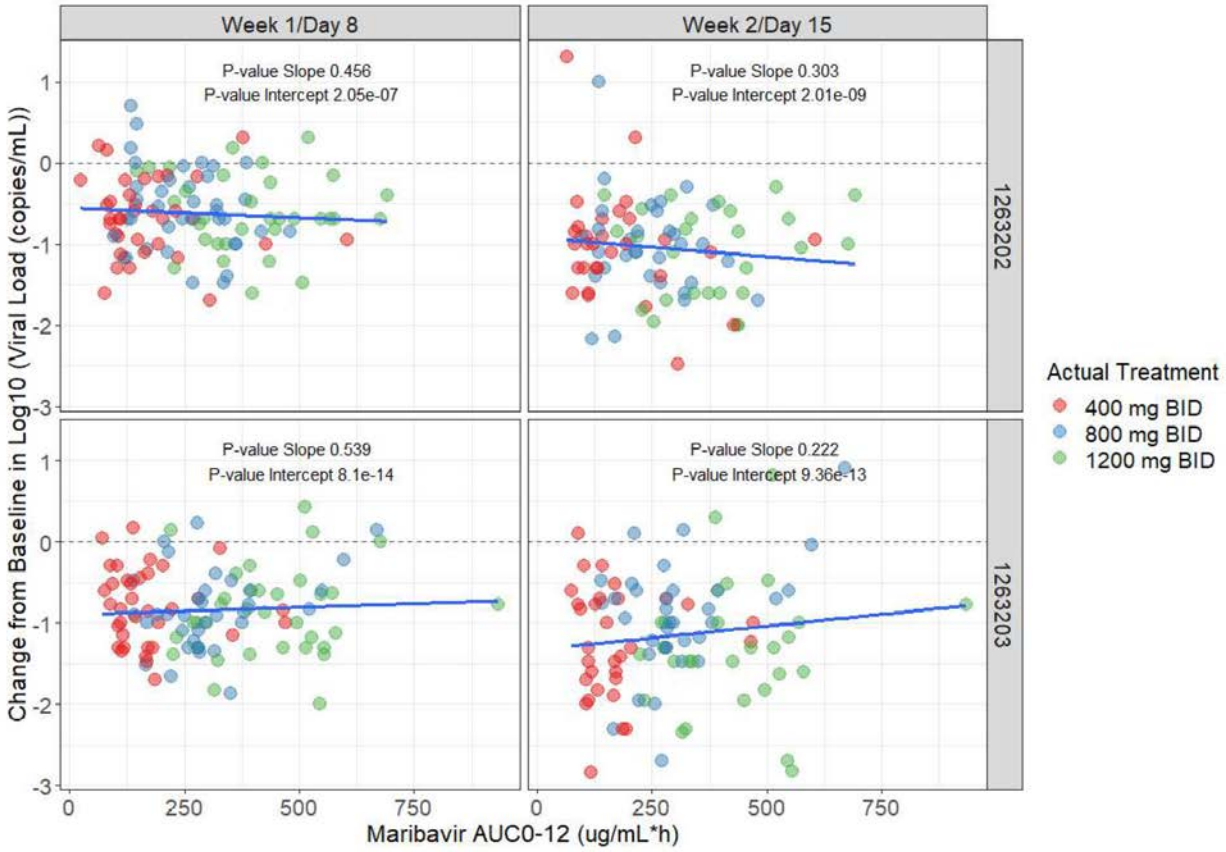
The Applicant conducted exposure-response analysis using the data from the two dose ranging studies that evaluated different doses of maribavir (400, 800, and 1,200 mg BID) for treatment of CMV infections in solid organ transplant and hematopoietic stem cell transplant recipients. Exposure parameters ($AUC_{0\text{-}12h}$, C_{max}, and minimum concentration [C_{min}]) of maribavir were estimated for each subject based on a population PK model. E-R analyses were performed by univariate analysis for the following endpoints by study:

- Viral load at Week 1 and 2: A linear regression was performed to assess E-R relationship for the change from baseline viral load were explored at Week 1 (Day 8) and Week 2 (Day 15). Patients with undetectable viral load (<200 copies/mL) at baseline were removed from the analysis.
- Undetectable plasma CMV DNA: Logistic regression models were constructed to assess E-R relationship for the probability of observing an undetectable plasma CMV DNA response (at any time) and a time-to-event analysis accounting for censoring of information was performed (Kaplan-Meier plots) to assess the relationship between exposure tertiles of maribavir exposure and the time to undetectable plasma CMV DNA response (first instance).
- Recurrence: Logistic regression models were constructed to assess E-R relationship for the probability of recurrence and a time-to-event analysis accounting for censoring of

information was performed (Kaplan-Meier plots) to assess the relationship between exposure tertiles of maribavir exposure and the time to recurrence.

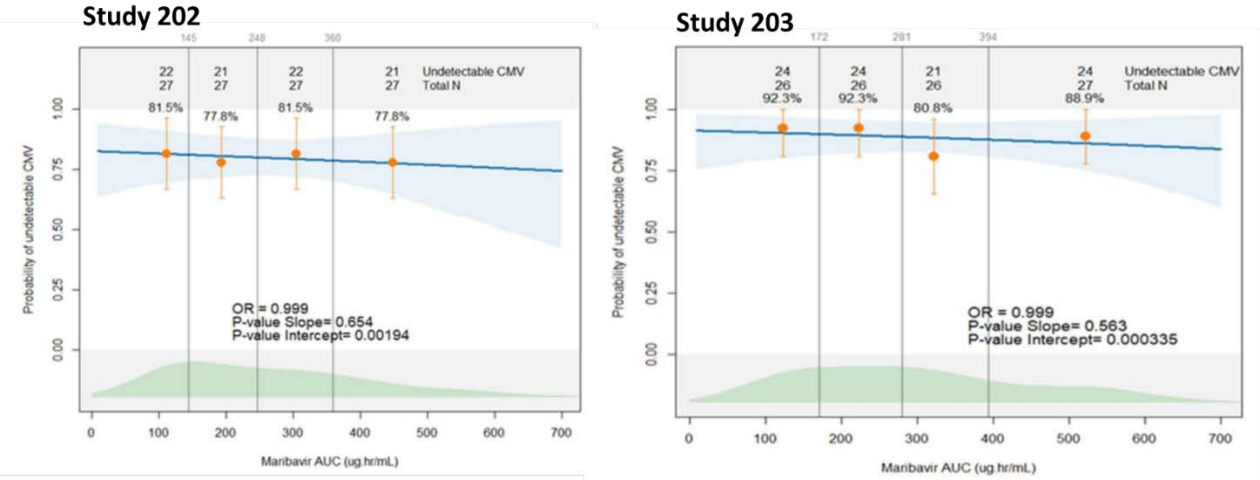
No statistically significant E-R relationships were observed for the change from baseline viral load at Week 1 and 2 and the probability of observing undetectable plasma CMV DNA response at any time, suggesting that lower and higher exposure of maribavir (AUC_{0-12}, C_{max} and C_{min}) achieved at the studied doses (400, 800, and 1,200 mg BID) were associated with similar effects. See Figure 25 and Figure 26.

Figure 25. Change From Baseline in Viral Load Versus AUC_{0-12} of Maribavir



Source: Applicant's Phase 2 Pharmacokinetics-Pharmacodynamics Report, Figure 8; page 18.
Abbreviations: AUC_{0-12}, area under the curve from 0-12 h; BID, twice daily

Figure 26. Probability of Undetectable Plasma CMV DNA Versus AUC_{0-12} of Maribavir



Source: Applicant's Phase 2 Pharmacokinetics-Pharmacodynamics Report, Figure 9; page 19.
Abbreviations: AUC_{0-12}, area under the curve from 0-12 h; CMV, cytomegalovirus; DNA, deoxyribonucleic acid; OR, odds ratio

In Trial 202, a statistically significant E-R relationship was observed for the probability of recurrence (higher maribavir exposures were associated with a higher probability of recurrence). This trend was not seen in Trial 203. No E-R relationships were observed for the time to recurrence in Studies 202 and 203. Patients with maribavir-resistant virus at baseline had more instances of recurrence relative to patients without resistant virus at baseline.

Reviewer's comments: The results of Applicant's E-R analysis with Phase 2 studies were generally consistent with those observed in dose-response for Studies 202, and 203, whereas no dose-response relationships were observed in dose range (400 mg BID to 1,200 mg BID) and supported dose selection (400 mg BID) for Phase 3 study (302). Because of the differences in study design, population, treatment duration, and background therapy, pooling E-R analysis of these 2 studies is not feasible.

Applicant's E-R analysis of Trial 202 suggests an association of higher maribavir exposures and the higher recurrence rate. This is consistent with the dose-response relationship for recurrence observed in Trial 202, where the higher recurrence rate was observed with 800 mg BID, and 1,200 mg BID arms compared to 400 mg BID. In the Applicant's E-R analysis, the Applicant used steady-state maribavir exposures derived from a PopPK model, which did not account for the actual dosing history (i.e., discontinuation of treatment during the trial) for each subject hence, this analysis is not readily interpretable.

Exposure-Response Analysis for Efficacy: Phase 3 Study (Trial 303)

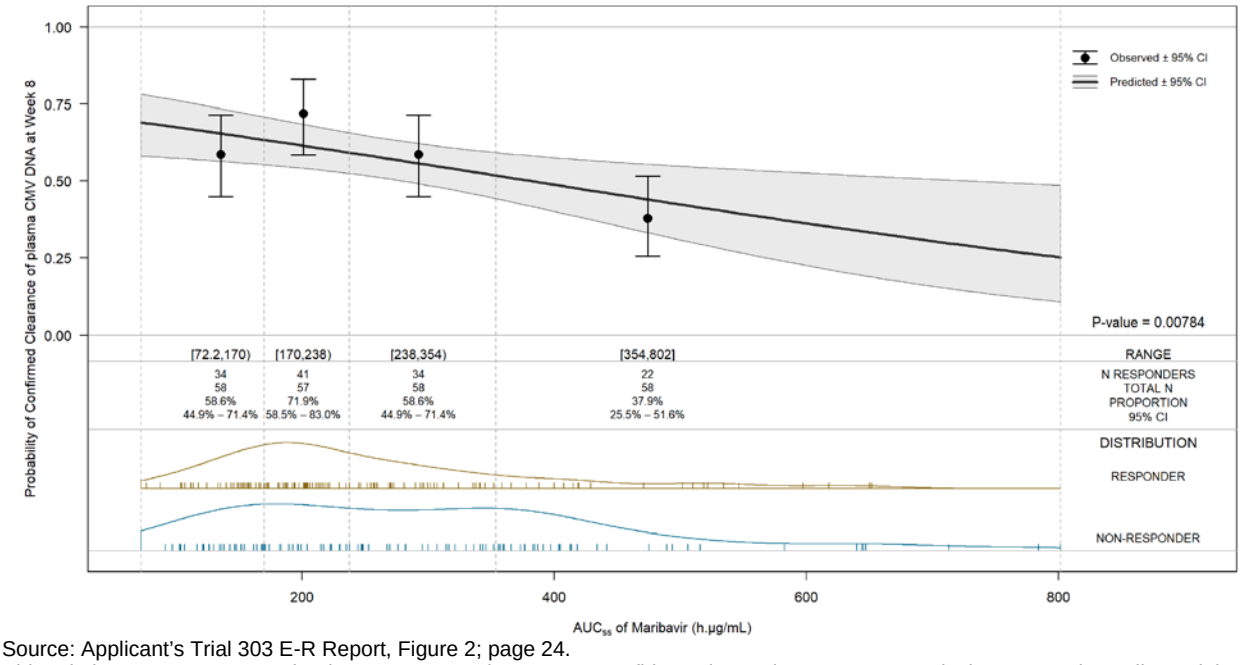
E-R analysis for efficacy was performed using efficacy and PK data from adult transplant recipients with CMV infections in Trial 303 at single dose level (400 mg BID). The PK data were available for a total 254 patients treated with maribavir including 232 patients assigned to receive maribavir, and the other 22 patients received maribavir as a rescue therapy. E-R analysis was performed based on a total of 231 patients from the PK set who were enrolled in the maribavir arm and had PK exposure parameters.

Maribavir exposure metrics used in the E-R analysis were AUC_{ss} (AUC from 0 to 24 hours on the last day of exposure), $C_{max,ss}$ (maximum concentration on the last day of exposure), and the

minimum concentration on the last day of exposure). These metrics were derived using the posterior Bayes parameters of the Applicant's final PopPK model. Actual dosing history and factors impacting the PK of maribavir (i.e., body weight, time-varying presence of strong CYP3A inhibitors or strong CYP3A inducers) were considered in the simulations. Efficacy variables for E-R analysis was the confirmed undetectable plasma CMV DNA (<LLOQ) at the end of Study Week 8 (primary endpoint) and the confirmed CMV viremia clearance and CMV infection symptom control at Study Week 8 followed by maintenance through Week 16 (secondary endpoint). Logistic regression analyses were performed to explore potential associations between maribavir exposure and the probability of response.

Univariate relationship between the probability of confirmed CMV clearance of plasma CMV DNA at Week 8 and the AUC_{ss} of maribavir shows an apparent negative E-R relationship (Figure 27). Similar trends were observed for $C_{max,ss}$ and the minimum concentration on the last day of exposure as exposure metrics. The similar trend was also observed with the secondary efficacy variable (confirmed CMV viremia clearance and CMV infection symptom control at Study Week 8 followed by maintenance through Week 16).

Figure 27. Univariate E-R Relationship for Confirmed Clearance of Plasma CMV DNA at Week 8



Source: Applicant's Trial 303 E-R Report, Figure 2; page 24.
Abbreviations: AUC_{ss}, area under the curve at steady state; CI, confidence interval; CMV, cytomegalovirus; DNA, deoxyribonucleic acid; E-R, exposure-response

The Applicant further conducted covariate analyses and identified treatment-emergent CMV substitution conferring resistance and cluster of differentiation (CD)4^+CD69^+ cell count at baseline resulted as significant predictors for the response variable. Patients with treatment-emergent CMV substitution were associated with a lower probability of response. Patients with $CD4^+CD69^+$ cell count of ≥0.5 to <2 were associated with a higher probability of response. Table 105 shows the parameter estimates for final logistic regression model.

Table 105. Multivariate Logistic Regression Analysis Parameters for Confirmed Clearance of Plasma CMV DNA at Week 8

Parameters	Estimate	SE	OR	95% CI OR	p-value
Intercept	0.674	0.513	-	-	0.189
AUC_{ss} of maribavir – increment of 10 µg.h/mL	-0.0254	0.0114	0.975	(0.953, 0.997)	0.0267
Treatment-emergent CMV mutation conferring resistance to maribavir [N=44]	-4.60	1.03	0.0101	(0.00133, 0.0766)	< 0.001
CD4+CD69+ cell count at baseline ≥ 0.5 - < 2 [N=42]	1.92	0.648	6.85	(1.92, 24.4)	0.00298
≥2 [N=12]	1.27	0.887	3.57	(0.628, 20.3)	0.151
Not reported [N=151]	0.718	0.484	2.05	(0.7194, 5.30)	0.138

Source: Applicant's Trial 303 Exposure-Response Report, Figure 2; page 24.
Reference subject had no treatment-emergent CMV substitution genes conferring resistance to mar bavir and had $CD4^{+}CD69^{+}$ cell count of <0.5 at baseline.
Abbreviations: AUC_{ss}, area under the curve at steady state; CD, cluster of differentiation; CI, confidence interval; CMV, cytomegalovirus; OR, odds ratio; SE, standard error

A statistically significant decreasing E-R relationship was observed between maribavir AUC_{ss} and the probability of confirmed CMV clearance of plasma CMV DNA at Week 8 with an estimated exponent of -0.0254 on the logit scale 10 µg·h/mL increment (p=0.0267), which corresponds to an odds ratio of 0.975 (95% CI [0.953, 0.997]). The Applicant notes that the apparent negative E-R relationship was primarily driven by the low probability of response in patients with treatment-emergent CMV substitutions who also presented higher exposure to maribavir. Lower proportions in the 1st and 2nd quartiles (i.e., 10.3% and 14.0%) developed treatment-emergent CMV substitutions conferring resistance to maribavir, compared to the 3rd and 4th quartiles (27.6% and 24.1%). Sensitivity analysis of univariate logistic regression excluding the subjects with treatment-emergent (TE) CMV substitutions shows that the E-R relationship is not statistically significant (p=0.0517). See Table 106.

Table 106. TE CMV Substitutions for Maribavir Resistance by Maribavir Exposure Quartiles

TE CMV Substitution for Maribavir Resistance	Maribavir AUC_{ss} (µg·h/mL) Quartiles			
	Q1 [72.2,170) (N=58)	Q2 [170,238) (N=57)	Q3 [238,354) (N=58)	Q4 [354,802] (N=58)
No, n (%)	52 (89.7%)	49 (86.0%)	42 (72.4%)	44 (75.9%)
Yes, n (%)	6 (10.3%)	8 (14.0%)	16 (27.6%)	14 (24.1%)

Source: Adapted from Applicant's Trial 303 E-R Report, Figure 12.8; pages 55-56.
Abbreviations: AUC_{ss}, area under the curve at steady state; CMV, cytomegalovirus; N, number of subjects in quartile; n, number of subjects within specified category Q, quartile; TE, treatment-emergent

Reviewer's comments: Applicant's E-R analysis based on the Phase 3 study is acceptable to describe the observed E-R relationship. Overall, at the proposed dose level 400 mg BID, increasing maribavir exposures is not associated with increasing response. This is consistent in the dose-response relationship observed in dose raging trials (Trials 202 and 203) across the dose levels 400 mg to 1,200 mg BID.

The Applicant suggested that the correlation between the maribavir exposures and TE CMV substitutions drives the negative E-R relationship. However, even when the univariate analyses were performed based on subset of patients excluding the subjects with TE substitutions, there is

a negative trend with a similar magnitude of odds ratio: adds ratio =0.979 (p =0.0517) per 10 μg·h/mL increment in AUC with the subset, compared to odds ratio =0.974 (p=0.00784) with all data. There is no physiologically plausible explanation for the correlation between higher maribavir exposure and TE substitutions.

E-R analysis also indicated that TE substitutions were a significant contributor to treatment failure: Only one subject of 44 with treatment-emergent CMV substitution was a responder (2.3%). Maribavir resistance-associated substitutions (RAS) causes large degrees of shift in the half maximal effective concentration (EC_{50}) values (Refer to Clinical Virologic Assessment), which is not expected to be overcome by any practical dose increase.

Applicant's Exposure-Response for Safety

The Applicant performed E-R analyses of safety based on data collected in Trial 303 using logistic regression modeling accounting for other risk factors impacting exposure-safety relationships. The exposure-safety population included patients with at least 1 measurable concentration of maribavir, which corresponds to the PK set population (maribavir arm, n=231). logistic regression models. Exposure variables assessed were the model-derived: AUC from 0 to 24 hours on the day of the adverse event (AE), maximum concentration from 0 to 24 hours on the day of the AE, average plasma concentration on each study day, AUC_{ss}, and $C_{max,ss}$. Safety variables were the probability of treatment-emergent AEs during the 8-week treatment phase: the probability of the following treatment-emergent AEs were explored based on the frequency (>10% of the PK population), severity or their special interest: taste disturbance, nausea, neutropenia, diarrhea, vomiting, viral infections, anemia, fatigue, pyrexia, renal disorder, immunosuppressant drug concentration level increased, and thrombocytopenia. In addition, the relationships between maribavir model-derived PK exposure metrics and treatment-emergent serious adverse events (SAEs) as a single category were also investigated.

Logistic regression analyses shows positive E-R relationships between the probability of fatigue and all exposure metrics with strongest relationship observed with $C_{max,ss}$. The effect of maribavir AUC_{ss} on the probability of SAEs was statistically significant ($p<0.001$) with observed probability of response of 29.3%, 35.1%, 34.5% and 53.4% for 1^{st}, 2^{nd}, 3^{rd}, and 4^{th} quartiles of exposure. A negative relationship ($p<0.05$) was observed between probability of taste disturbance and average plasma concentration on each study day of maribavir. None of the other AEs had a significant relationship with maribavir exposures.

Reviewer's comment: For dose-safety relationships, refer to Clinical Safety Assessment. Applicant's exposure-safety analysis based on the single dose level (400 mg BID) suggests fatigue is exposure dependent (adjusted odds ratio =1.09 per 1 μg/mL increment in $C_{max,ss}$). Considering the observed variability (% coefficient of variation of 39%) of maribavir exposures and the mean $C_{max,ss}$ (17 μg/mL) following the proposed dosing regimen, this trend is not considered clinically meaningful to warrant dose adjustment. The Applicant's exposure-safety analysis for SAE is considered as exploratory as any meaningful inference cannot be made based on the pooled SAEs where a treatment-emergent SAEs were treated as a single category as the safety variable. Formal E-R analysis for distinct SAEs is not feasible due to the small incidence rate for each SAE.

14.4.3. Use in Adolescents

Maribavir trials did not include subjects <18 years of age, and no PK data are available for subjects 12 to 18 years of age in the completed or ongoing clinical trials at the time of this review. The range of body weights of adult subjects in clinical trials was 36 to 140 kg and the Applicant's population PK analysis based on adult patient data showed that body weight is not a significant covariate for maribavir PK.

Per the Agency's request, the Applicant conducted population PK modeling/simulations based on the adult population PK model, and predicted maribavir exposures for the expected weight range for adolescent subjects. Simulations were conducted with the following two models to account for the uncertainty of application of the adult PopPK model to predict adolescent exposures:

- Original PopPK model (Section 14.4.1): a model describing body weight effect using traditional allometric exponents of 0.75 for clearances and 1 for volumes of distribution
- Revised PopPK model: a model describing body weight effect using the estimated allometric exponents based on adult PK data. The original model was re-run to estimate the weight exponents. Parameter estimates for this model is presented in Table 107.

Table 107. Parameter Estimates of the Revised PopPK Model

Parameter	Units	NONMEM Estimates			
		Estimate[a]	%RSE[b]	95% CI[a]	IIV CV%[c] (%RSE)
CL/F	L/hr	3.90	3.62	3.63 to 4.18	50.0 (6.44)
Vc/F	L	19.0	3.73	17.7 to 20.4	32.8 (22.1)
Q/F	L/hr	0.826	14.5	0.622 to 1.10	88.1 (40.1)
Vp/F	L	8.51	10.3	6.95 to 10.4	102 (24.9)
Ka	hr^{-1}	0.301	10.1	0.247 to 0.367	166 (12.4)
Lag-time	hr	0.264	7.01	0.230 to 0.303	37.9 (38.9)
CL/F~weight	unitless	0.114	74.8	-0.0530 to 0.281	-
Vc/F~weight	unitless	0.407	23.7	0.218 to 0.595	-
Q/F~weight	unitless	1.95	21.7	1.12 to 2.78	-
Vp/F~weight	unitless	0.663	64.0	-0.169 to 1.49	-
CL/F~CYP3A strong inhibitors	unitless	0.701	2.01	0.674 to 0.729	
CL/F~CYP3A strong inducers	unitless	2.24	2.61	2.13 to 2.36	
Ka~dose	unitless	-2.09	4.39	-2.27 to -1.91	
CL/F~ transplant patients with CMV	unitless	0.755	4.22	0.695 to 0.820	
$\sigma^2_{prop\ Phase\ 1}$	unitless	0.0672	2.81	0.0635-0.0709	25.9[d]
$\sigma^2_{prop\ Phase\ 2\ \&\ 3}$	unitless	0.137	3.71	0.127-0.147	37.1[d]

Source: Applicant's information request response dated October 22, 2021.
Abbreviations: CI, confidence interval; CL/F, apparent clearance; CMV, cytomegalovirus; CYP, cytochrome P450; IIV, interindividual variability; Ka, dissociation constant; NONMEM, nonlinear mixed effects modeling; Q/F, apparent intercompartmental clearance; RSE, relative standard error; Vc/F, apparent volume of distribution in the central compartment; Vp/F, apparent volume of distribution in the peripheral compartment

Reviewer's comments: Though the weight effects on both CL/F and Vp/F were poorly estimated (relative standard error >50%) and the 95% CIs for both estimates included the null value (0), based on the goodness-of-fit plots and ETA-covariate relationships, this model was used to perform a sensitivity simulation to address the uncertainty in the original model which used the traditional allometry approach that are not supported by the adult PK data (refer to Section 14.4.1).

The steady-state exposures ($AUC_{0-\tau}$, C_{max} and C_{min}) following 400 mg BID in adults with CMV based on the original model are presented in Table 108.

Table 108. Steady-State Maribavir Exposures for Phase 3 Adult Transplant Patients With the Original PopPK Models

Population	Dose (mg BID)	Statistic	Original PopPK model ("Run 171")		
			$AUC_{0-\tau}$ (µg·h/mL)	$C_{max,ss}$ (µg/mL)	$C_{min,ss}$ (µg/mL)
Phase 3 Transplant Patients With CMV	400 mg BID	n	253	253	253
		Mean (%CV)	145 (51.4)	18.1 (39.9)	6.80 (76.4)
		Geometric mean (%CV)	129 (51.6)	16.9 (39.1)	5.13 (93.0)
		Median	123	16.7	5.26
		5th percentile	57.0	9.16	1.18
		10th percentile	71.1	10.3	1.83
		20th percentile	84.7	12.4	2.88
		25th percentile	93.3	13.0	3.17
		75th percentile	187	21.8	8.90
		80th percentile	201	23.5	9.79
		90th percentile	238	27.8	13.2
		95th percentile	291	31.2	18.3

Source: Applicant's IR response dated October 22, 2021.
Abbreviations: $AUC_{0-\tau}$, area under the curve from time zero to last dose; $C_{max,ss}$, maximum concentration at steady state; $C_{min,ss}$, minimum concentration at steady state; CMV, cytomegalovirus; CV, coefficient of variation; PopPK, population pharmacokinetics

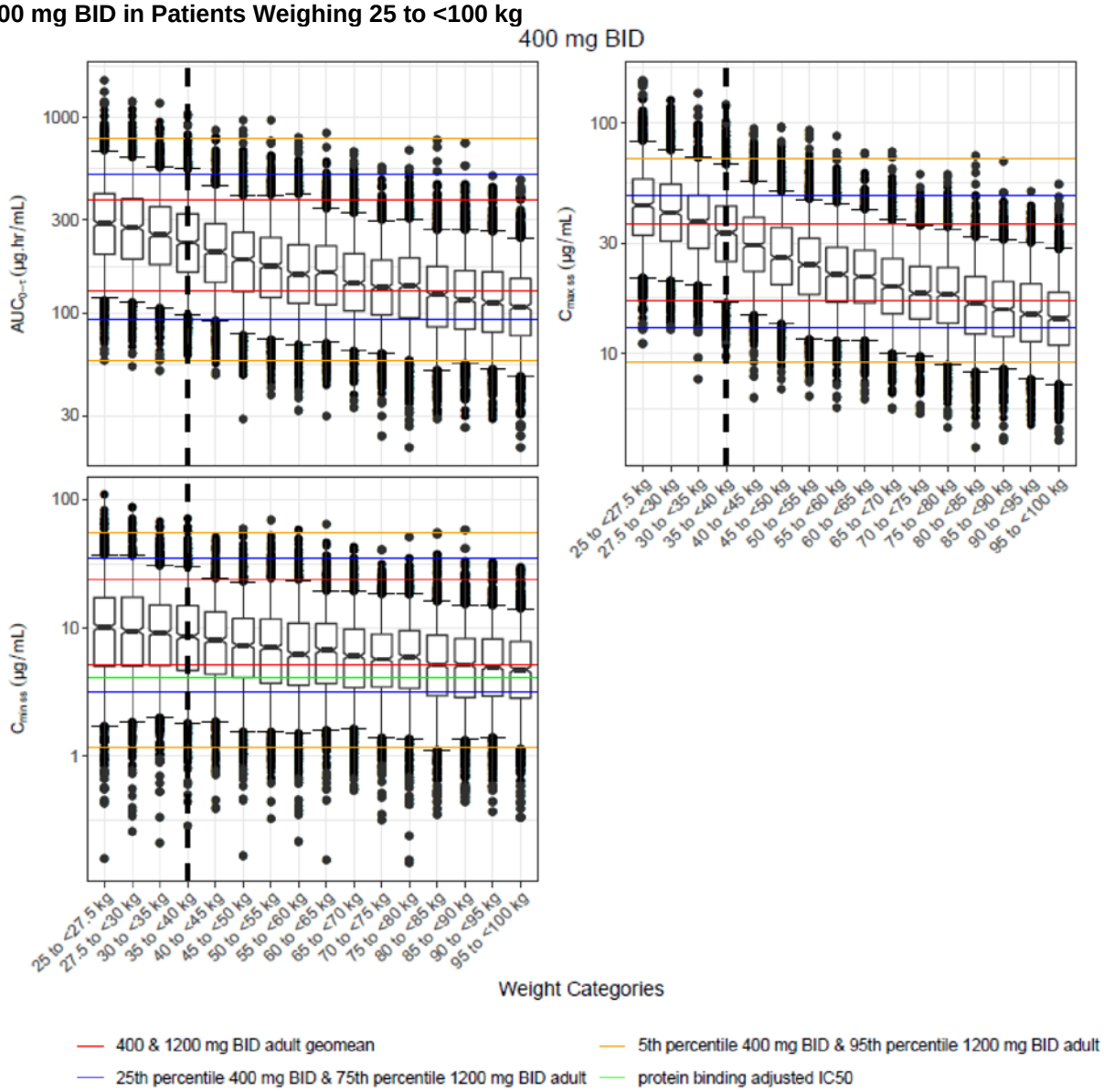
Maribavir exposure generally increases as body weight decrease and the magnitude in exposure increases is more prominent with the original PopPK model (Figure 28) than the revised PopPK model (Figure 29). With the original PopPK model, geometric means of $AUC_{0-\tau}$ are predicted to be 229, 206, and 184 h*µg/mL for 35 to <40 kg, 40 to <45 kg, and 45 to <50 kg subjects, respectively, and geometric means of $C_{max,ss}$ are 33.3, 29.5, and 26.2 µg/mL for 35 to <40 kg, 40 to <45 kg, and 45-<50 kg subjects, respectively. With the revised PopPK model, $AUC_{0-\tau}$ and C_{max} across all body weight groups are similar to those in adults.

For safety concerns, a worst exposure scenario could be subjects weighing 35 to 40 kg when the original model can genuinely describe adolescent PK. In this scenario, the mean $AUC_{0-\tau}$ and C_{max} for subjects weighing 35 to 40 kg are predicted to be <2 fold of those in adult patients.

For efficacy concerns, with both modeling approaches, the fraction of subjects ≥35 kg administered the adult dose with C_{min} below the adult 5th percentile at a dose of 400 mg BID was <10%.

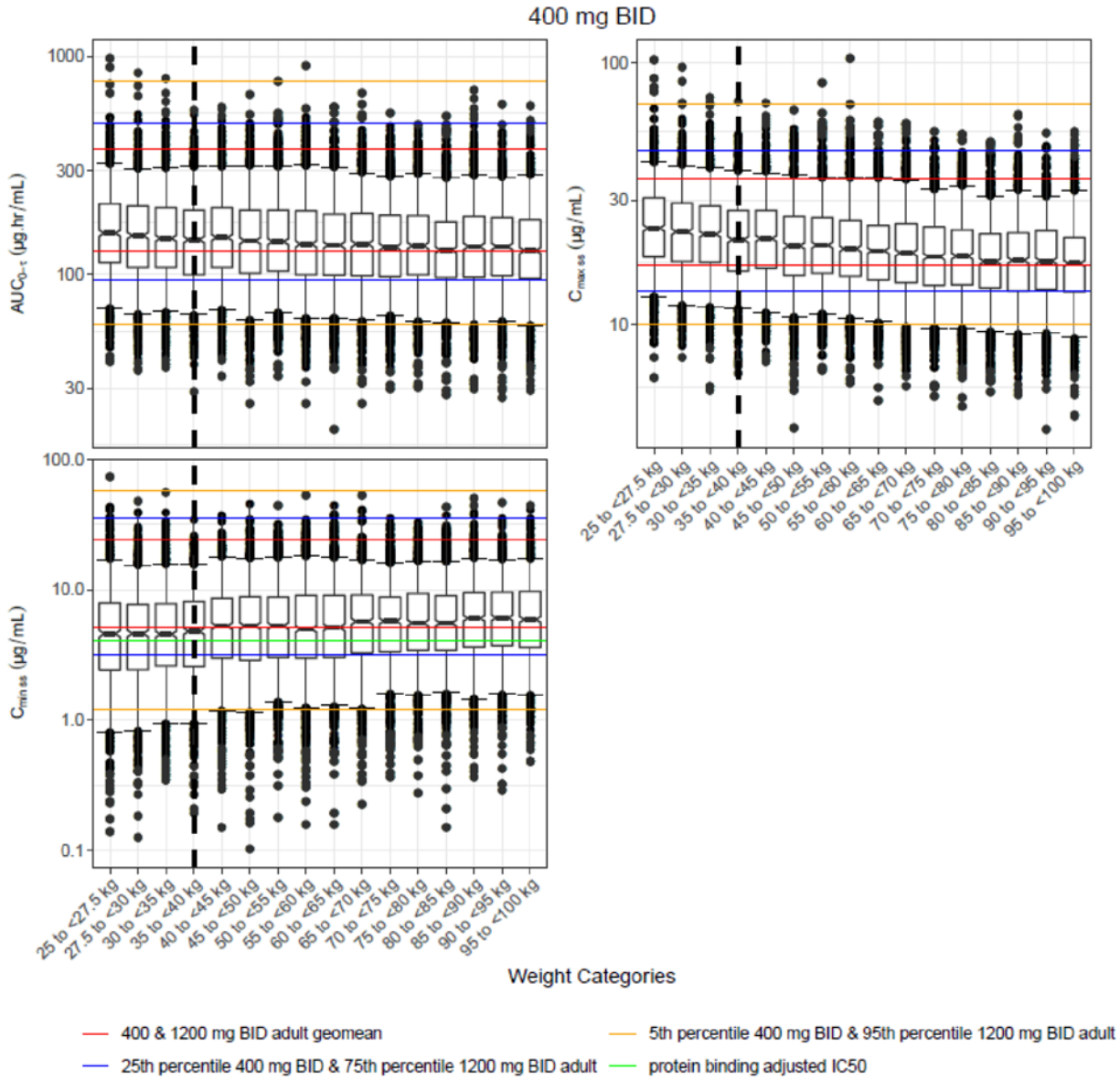
Given that the model-predicted exposures in adolescent patients are generally contained within those observed in adult patients, and that CYP3A activity is expected to be mature by age 12, the proposed dosing regimen (400 mg BID) is expected to provide similar exposures in adolescents (age ≥12 years and ≥35 kg) compared to those in adults.

Figure 28. Predicted Steady-State Maribavir Exposure Using the Original PopPK Model Following 400 mg BID in Patients Weighing 25 to <100 kg



Source: Applicant's information request response dated October 22, 2021.
Abbreviations: $AUC_{0-\tau}$, area under the curve from time zero to last dose; BID, twice daily; $C_{min,ss}$, minimum concentration at steady state; IC50, 50% inhibitory concentration; PopPK, population pharmacokinetics

Figure 29. Predicted Steady-State Maribavir Exposure Using the Revised PopPK Model Following 400 mg BID in Patients Weighing 25 to <100 kg



Source: Applicant's information request response dated October 14, 2021.
Black center line of the box represents median, top and base of the box represent inter-quartile range. Whiskers represent 5th and 95th percentiles. Outliers beyond 5th and 95th percentiles are represented by closed circles. The lower and upper red horizontal lines represent the adult geometric mean at 400 and 1,200 mg BID dose in adult CMV patients, respectively. The lower and upper yellow horizontal lines denote the 5th percentile exposure at 400 mg BID and 95th percentile exposure at 1,200 mg BID dose in adult CMV patients, respectively. The lower and upper blue horizontal lines denote the 25th percentile exposure at 400 mg BID and 75th percentile exposure at 1,200 mg BID dose in adult CMV patients, respectively. Green horizontal line in the C_{min} boxplot represents the protein binding adjusted CMV UL97 IC50 of 4.1 µg/mL.
Abbreviations: AUC_{0-T}, area under the curve from time zero to last dose; BID, twice daily; $C_{min,ss}$, minimum concentration at steady state; CMV, cytomegalovirus; IC50, 50% inhibitory concentration; PopPK, population pharmacokinetics

14.4.4. PBPK Review

14.4.4.1. Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's following physiological based pharmacokinetic (PBPK) reports to support the intended uses.

- Quantitative prediction of the systemic exposure of maribavir using prior in vitro and in vivo data: potential for CYP3A4 mediated drug-drug interactions with maribavir as a victim (N10325M-SHP620).
- Expansion of the maribavir model within the Simcyp population-based simulator to include the Advance Dissolution Absorption and Metabolism model and subsequent evaluation of DDI liability as a perpetrator of breast cancer–related protein (BCRP)-mediated transport (TKD-BCS-01091-R1).

The Division of Pharmacometrics has reviewed the PBPK reports, supporting modeling files, and the Applicant's responses to the FDA's information request (IR) submitted on July 16, 2021, to conclude the following:

- The maribavir PBPK models were able to capture the observed maribavir PK following a single oral dose (400, 800 and 1,600 mg), or multiple oral dose administration (400 mg BID) in healthy subjects. In addition, the model was able to predict C_{trough} values when the experimental LLOQ of 0.2 µg/mL was applied to the simulated data.
- The maribavir PBPK models are adequate to predict the effect of diltiazem and erythromycin (moderate CYP3A inhibitors) on the PK of maribavir in healthy subjects. About 40% increase in maribavir AUC was predicted with erythromycin (500 mg TID), whereas the increase in maribavir AUC(9.0%) with diltiazem (60 mg TID) was deemed clinically insignificant.
- The maribavir PBPK models are adequate to predict the effect of ritonavir (a strong CYP3A inhibitor) on the PK of maribavir in healthy subjects. About 60% increase in maribavir AUC was predicted with ritonavir (100 mg BID).
- The maribavir PBPK models are adequate to predict the effect of phenobarbital and efavirenz (moderate CYP3A inducers) on the PK of maribavir in healthy subjects. The simulated maribavir AUC ratio, C_{max} ratio and C_{trough} ratio were 0.60, 0.72, and 0.44, respectively, with phenobarbital (100 mg QD), and 0.56, 0.74, and 0.34, respectively, with efavirenz (600 mg QD).
- The maribavir PBPK models are adequate to predict the effect of carbamazepine and phenytoin (strong CYP3A inducers) on the PK of maribavir in healthy subjects. The simulated maribavir AUC ratio, C_{max} ratio and C_{trough} ratio were 0.70, 0.77, and 0.54, respectively, with carbamazepine (400 mg QD), and 0.57, 0.68, and 0.40, respectively, with phenytoin (300 mg QD).
- In vitro study and PBPK modeling efforts suggest the DDI potential of maribavir with rosuvastatin (a BCRP substrate) cannot be excluded.

14.4.4.2. Applicant's PBPK Modeling Effort

PBPK Software

Simcyp V17 (Simcyp Ltd., United Kingdom) was used to develop the maribavir PBPK models and predict the PK of maribavir with and without CYP3A modulators, and the effect of maribavir on the PK of rosuvastatin.

Model Development

Maribavir Model 1

Maribavir model 1 was used to assess the DDI potential of maribavir with CYP3A modulators. The first order absorption model was used to describe the absorption of maribavir. The fraction absorbed (0.90) and absorption rate constant (1.2 h^{-1}) were optimized based on the clinical PK data (Study VP1612).

The maribavir fraction unbound in plasma was 0.0129. A full PBPK model was used to simulate the distribution phase of maribavir PK profiles. The volume of distribution at steady state was predicted using the Method 3 (Rodgers and Rowland model with ion membrane permeability) in Simcyp. A volume of distribution at steady state value of 0.265 L/kg with an equilibrium constant scalar of 0.55 was optimized using clinical PK data (Study VP1671).

A retrograde approach was used to calculate the hepatic intrinsic clearance (80 µl/min/mg protein) based on the in vivo apparent clearance (CL/F) value of 4.57 L/h, which was derived from clinical PK data after a single dose of 400 mg maribavir (Study VP1612). Maribavir is a substrate of CYP3A4 and CYP1A2. Based on the in vitro depletion data generated in the phenotyping study and chemical inhibition study results, the CYP3A4 and CYP1A2 mediated hepatic intrinsic clearance was calculated. Then, the fractional contributions of CYP3A and CYP1A2 were estimated to be 0.35 and 0.04, respectively. Multiple uridine 5'-diphospho-glucuronosyltransferase enzymes (UGT1A1, UGT1A3, UGT2B7 and UGT1A9) were also involved in the metabolism of maribavir. The rate of depletion of maribavir in in vitro study systems (liver microsomes and recombinant enzymes) was too low to determine the intrinsic clearance value for uridine 5'-diphospho-glucuronosyltransferase enzymes. Therefore, the uridine 5'-diphospho-glucuronosyltransferase elimination pathways were lumped into an additional hepatic clearance, representing 0.61 of total clearance.

Following oral administration, VP 44469 was the major and inactive metabolite. The mass balance study showed that maribavir and VP44469 concentrations accounted for all the radioactive material observed in plasma during the first 24 hours after administration. The VP 44469 to maribavir AUC ratios from 0 to infinity ranged from 0.15 to 0.20.

VP 44469 accounted for 34.0% and 7.2% of the dose administered in urine and feces, respectively. The unchanged parent drug accounted for 1.8% and 5.7% of the dose administered in urine and feces, respectively. Renal clearance of 0.051 L/h (CMAB1001) was included in the model.

Maribavir Model 2

Maribavir model 2 was used to evaluate the DDI potential of maribavir as a perpetrator with a BCRP substrate.

In maribavir model 2, the absorption model was changed from first order absorption model (Maribavir model 1) to Advance Dissolution Absorption and Metabolism model. Intrinsic solubility and dissolution constant were estimated using Simcyp In Vitro Analysis Toolkit (SIVA, version 4.0) based on the solubility data and dissolution data, respectively. Mechanistic effective permeability model was used to model the absorption of maribavir in the gastrointestinal tract.

Maribavir has been identified as a P-gp, BCRP and OATP1B1/1B3 inhibitor in vitro. In vitro obtained inhibitory constant (Ki) values for P-gp, BCRP and OATP1B1/1B3 were used in the model to evaluate the DDI potential of maribavir with a BCRP substrate. The Ki value for P-gp was verified based on the clinical data with digoxin. An in vitro obtained Ki value (33.8μM) and a Ki value (1.2μM) estimated using SIVA 4.0 modeling for P-gp were applied in the model to simulate the effect of maribavir on the PK of digoxin. The results showed that both Ki values resulted in simulated digoxin C_{max} and AUC ratios were within 1.5-fold of the observed data. Thereafter, two different Ki values for BCRP (an in vitro obtained Ki value ([(b) (4)]μM) and a Ki value ([(b) (4)]μM) estimated using SIVA 4.0) were applied in the model to assess the effect of maribavir on the PK of the BCRP substrate rosuvastatin. In addition, the effect of different BCRP phenotypes in subpopulations on the maribavir mediated inhibitory effect on rosuvastatin PK was also evaluated.

The model structure and parameter values in Model 2 remained the same as those in Model 1 with respect to the characterization of maribavir distribution, metabolism, and elimination processes.

Victim Drug Models

The default PBPK models of ketoconazole, ritonavir, diltiazem, erythromycin, rifampin, carbamazepine, phenytoin, phenobarbital, efavirenz, and rosuvastatin in Simcyp (V17) were used for DDI predictions.

FDA's Assessment

(1) The fraction metabolized estimation was based on the experimental results with CYP inhibitors in the study SHI-5895, where maribavir was incubated with human liver microsome for 1 hour, and only 3 metabolites (M333, M243, and M201) were identified. Based on the metabolic scheme provided in the Clinical Pharmacology Summary, there were a few metabolites, such as M5, M6, M14, which were not identified in Study SHI-5895 and may be formed via oxidation reaction. An information request was issued requesting the Applicant to discuss the impact on DDI prediction with carbamazepine (a strong CYP3A4 and CYP2B6 inducer) if other CYP enzyme (such as CYP2B6) was involved in the metabolism of maribavir.

(2) Maribavir dose adjustment with CYP3A inducers was based on the defined lower and upper no effect boundaries. The C_{trough} predictions were verified using the clinical DDI data with rifampin (Study 1263-110) and appeared to overpredict the rifampin mediated induction effect on C_{trough}. An information request was issued requesting the Applicant to provide justification that the current maribavir model is adequate to predict C_{trough}.

Applicant's Response to FDA's IR and Assessment

(1) In the response to the FDA's IR, the Applicant submitted a new in vitro study report where the targeted LC/MS/MS was used for sample analysis and showed that the formation of M5 and M6 was mainly mediated by recombinant human CYP3A4 and CYP1A2. M13 was formed from M14, which has been identified in the in vitro study (SHI-R5895). In addition, rifampin was considered as a moderate CYP2B6 inducer and thus the clinical DDI study results with rifampin represented the induction effect on multiple CYP enzymes, including CYP2B6, if CYP2B6 was involved in the metabolism of maribavir. These data, together with the model validation with the clinical DDI studies with ketoconazole and rifampin, suggested that the contribution of other CYP enzymes to the metabolism of maribavir may not be significant, and the impact on the DDI evaluation with carbamazepine would not be expected to be significant.

(2) In the response to the FDA's IR, the Applicant explained why the C_{trough} values with rifampin were underpredicted: "The bioanalytical method for the determination of the maribavir plasma concentrations in clinical study 1263-110 had a lower limit of quantification (LLOQ) of 0.2 µg/mL, which was not applied in the original PBPK simulations (N10325M-SHP620). Simulations in combination with rifampin resulted in a proportion of individual predicted C_{trough} values that were close to or below this LLOQ." In addition, the Applicant re-calculated the C_{trough} values after the concentrations below LLOQ were removed (Table 109). It appears that the model was able to predict the C_{trough} values within 1.25-fold after the experimentally LLOQ of 0.2 µg/mL was applied to the simulated data. It is worth noting that the lower bound of the 90% CIs for the simulated maribavir C_{trough} values, when coadministered with the CYP3A inducers, phenobarbital, phenytoin, and carbamazepine, were substantially higher than the LLOQ. Moreover, even if the maribavir C_{trough} values were underpredicted, when maribavir is coadministered with these CYP3A inducers, the argument that the true maribavir C_{trough} value is higher than 80% of steady-state C_{trough} at 400 mg BID dose would be valid, if the simulated C_{trough} value is higher than 80% of steady-state C_{trough} at 400 mg BID dose, the pre-defined lower no effect boundary.

Table 109. Simulated Arithmetic and Geometric Mean C_{trough} Ratios Following Administration of 400 mg BID Maribavir in Combination With 600 mg QD Rifampin

Maribavir + rifampin versus maribavir alone	Maribavir C_{trough} ratio No LLOQ applied	Maribavir C_{trough} ratio With LLOQ applied
Arithmetic Mean		
Simulated	0.094	0.19
Observed	0.17	0.17
Simulated/Observed	0.56	1.12
Geometric Mean		
Simulated	0.043	0.16
Observed	0.18	0.18
Simulated/Observed	0.24	0.90

Source: Study 1263-110 CSR Addendum 1, Table 10.A.1, Table 10.A.2, and Table 10.A.5; PBPK Report N10325M-SHP620, Table 7
Source: Applicant's response to FDA's Information Request.
Observed Values From Clinical Study 1263-110.
LLOQ of 0.2 µg/mL was or was not applied to the simulated data.
Abbreviations: BID, twice daily; C_{trough}, trough concentration; LLOQ, lower limit of quantitation; QD, once daily

PBPK Model Application

The developed PBPK model was used to simulate the DDI for maribavir in the following scenarios:

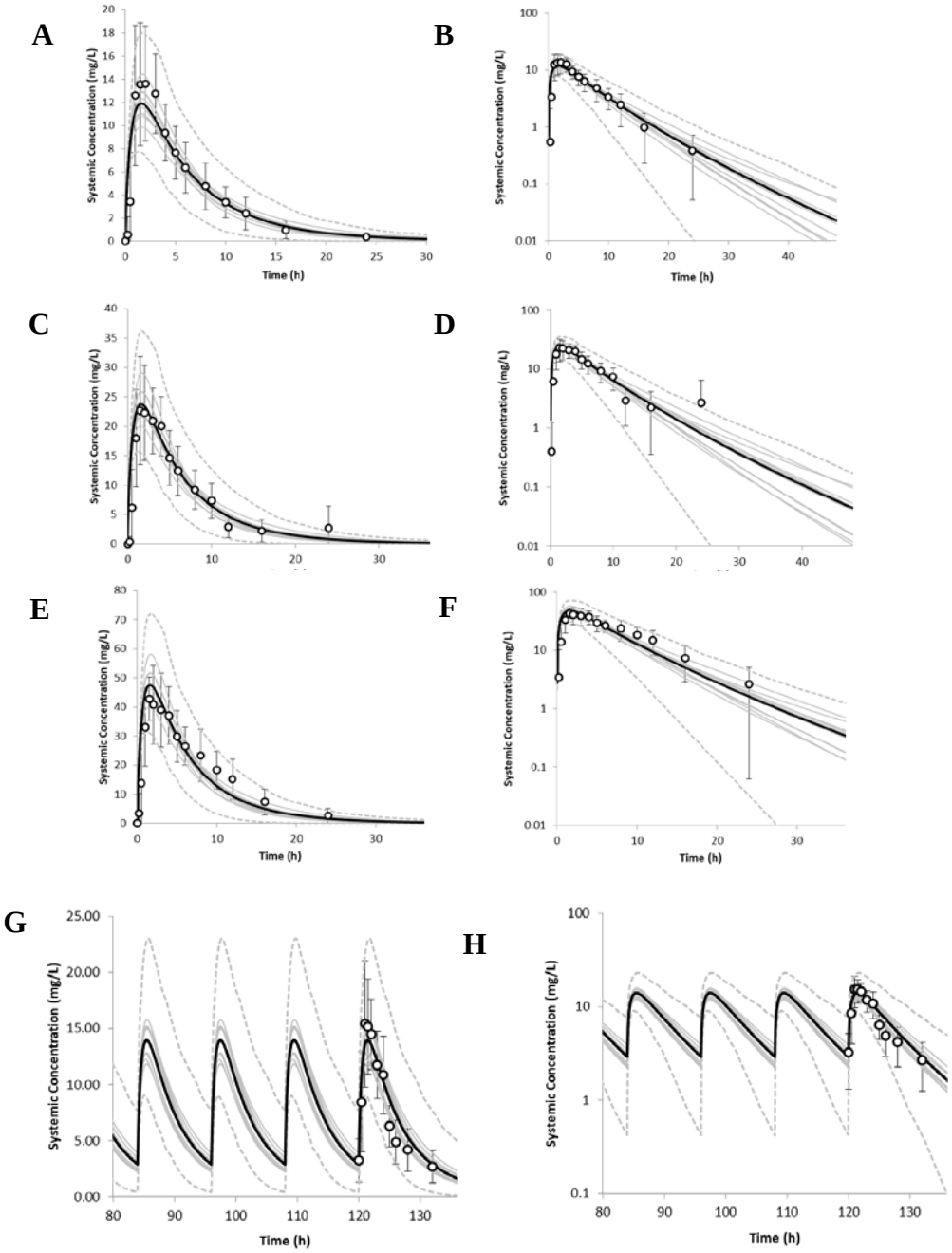
- To predict the effect of diltiazem and erythromycin (moderate CYP3A inhibitors) on the PK of maribavir following oral administration in healthy subjects.
- To predict the effect of ritonavir (a strong CYP3A inhibitor) on the PK of maribavir following oral administration in healthy subjects.
- To predict the effect of phenobarbital and efavirenz (moderate CYP3A inducers) on the PK of maribavir following oral administration in healthy subjects.
- To predict the effect of carbamazepine and phenytoin (strong CYP3A inducers) on the PK of maribavir following oral administration in healthy subjects.
- To predict the effect of maribavir on the PK of rosuvastatin (a BCRP substrate) following oral administration in healthy subjects.

Results

(1) Can the maribavir PBPK model describe maribavir PK in healthy subjects?

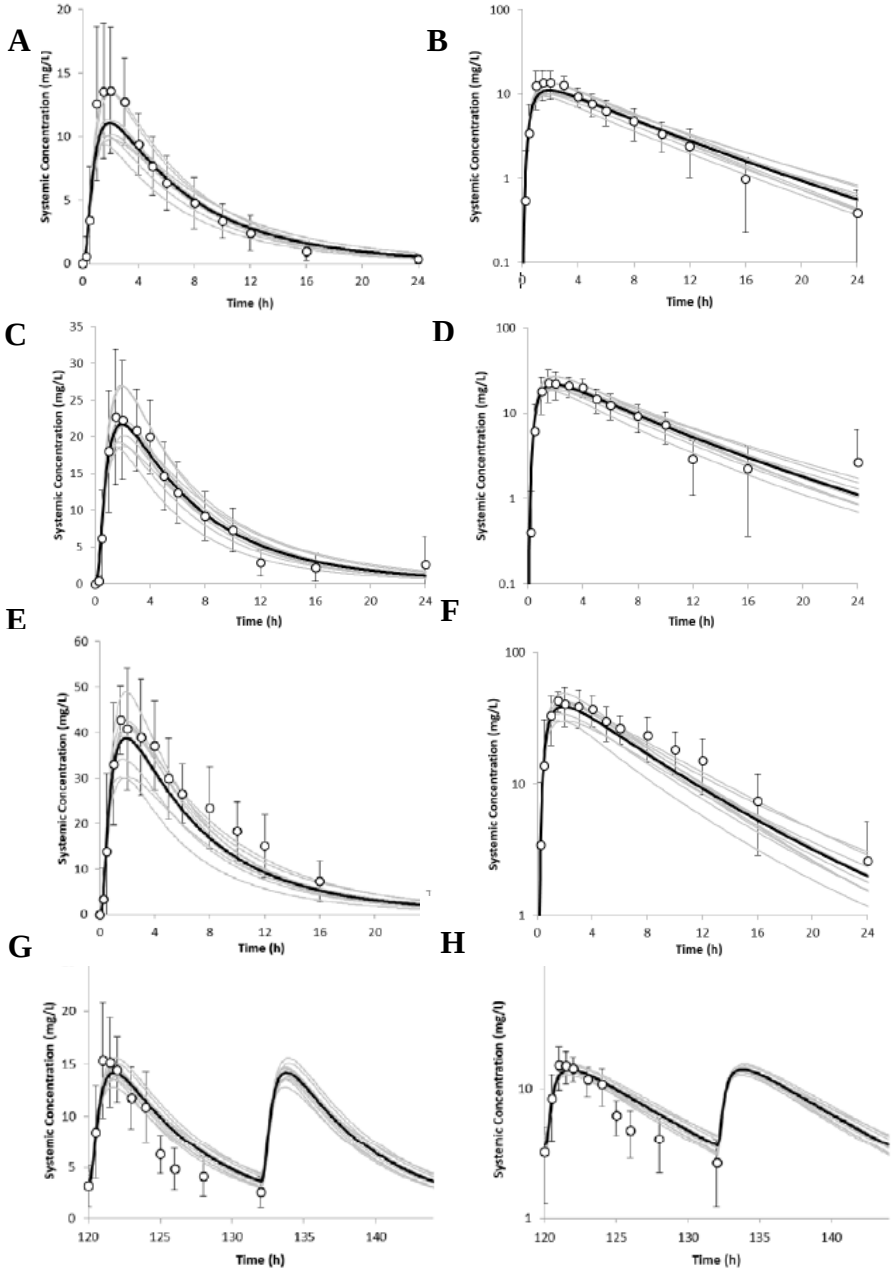
Yes. The maribavir model 1 and model 2 were able to capture the observed maribavir PK profiles following a single oral dose administration (400, 800 and 1,600 mg), or multiple oral dose administration (400 mg BID) in healthy subjects (Figure 30, Figure 31 and Table 110). In addition, Model 1 was able to predict geometric mean C_{trough} values when the experimental LLOQ of 0.2 mg/mL was applied to the simulated data (Table 109).

Figure 30. Mean Plasma Concentration-Time Profiles of Maribavir Following Maribavir Administration in Healthy Subjects



Source: Study CMAB1001 (A, B, C, D, E, and F) and Study 1263-110/VP1671 (G and H).
Lines are simulated data; circles are observed data.
Maribavir model 1 was used for the simulations.
A and B: single oral 400 mg dose
C and D: single oral 800 mg dose
E and F: single oral 1,600 mg dose
G and H: multiple (BID) oral 400 mg doses
A, C, and E: Linear Scale; B, D, and F: Logarithmic Scale
Abbreviation: BID, twice daily

Figure 31. Simulated (Lines) and Observed (Circles) Mean Plasma Concentration-Time Profiles of Maribavir Following Maribavir Administration in Healthy Subjects



Sources: Study CMAB1001 (A, B, C, D, E, and F) and Study 1263-110/VP1671 (G and H).
Lines are simulated data; circles are observed data.
Maribavir model 2 was used for the simulations.
A and B: single oral 400 mg dose
C and D: single oral 800 mg dose
E and F: single oral 1,600 mg dose
G and H: multiple (BID) oral 400 mg doses
A, C, and E: Linear Scale; B, D, and F: Logarithmic Scale
Abbreviation: BID, twice daily

Table 110. Maribavir Mean C_{max} and AUC Using Model 1 and Geometric Mean C_{max} and AUC Using Model 2 and C_{max} and AUC Ratios Following Single or Multiple Oral Doses of Maribavir

Dose, Route, Model	$AUC_{0-\infty}$ (mg*h/L) Observed/Predicted/$R_{Pred/Obs}$	C_{max} (mg/L) Observed/Predicted/$R_{Pred/Obs}$	Study Number
400 mg, SD, Model 1	97.9/97.8/1.00	16.7/11.9/0.72	CMAB1001
400 mg, SD, Model 2	94.3/91.9/0.97	15.9/10.9/0.69	
800 mg, SD, Model 1	183/195/1.07	26.4/24.1/0.91	
800 mg, SD, Model 2	173/177/1.02	25.5/21.4/0.84	
1,600 mg, SD, Model 1	437/391/0.90	48.8/48.1/0.99	
1,600 mg, SD, Model 2	412/316/0.77	48.2/38.0/0.79	
400 mg, BID, Day 5, Model 1	89.9/96.5/1.07[a]	16.9/14.3/0.85[b] 2.54/2.99/1.18[c]	1263-110/ VP1671
400 mg, BID, Day 5, Model 2	89.9/94.2/1.05[a]	16.9/13.8/0.82[b] 2.54/2.84/1.12[c]	

Source: observed data were from Study CMAB1001 and 1263-110/VP1671.
[a], AUC_{0-12}
[b], C_{max}
[c], C_{12h}
Abbreviations: AUC_{0-12}, area under the curve from time zero to 12 h; $AUC_{0-\infty}$, area under the curve from time zero to infinity; BID, twice daily; C_{12h}, concentration at 12 h; C_{max}, maximum concentration; SD, single dose

(2) Can the maribavir PBPK model predict the effect of diltiazem and erythromycin (moderate CYP3A inhibitors) on the PK of maribavir following oral administration in healthy subjects?

Yes. The maribavir model validated using clinical data with ketoconazole (a strong CYP3A inhibitor) and rifampin (a strong CYP3A inducer) was adequate to predict the effect of moderate CYP3A inhibitors (diltiazem and erythromycin) on the PK of maribavir following a single dose administration of maribavir and multiple dose administration of diltiazem or erythromycin in healthy subjects (Table 111).

(3) Can the maribavir PBPK model predict the effect of ritonavir (a strong CYP3A inhibitor) on the PK of maribavir following oral administration in healthy subjects?

Yes. The maribavir model validated using clinical data with ketoconazole (a strong CYP3A inhibitor) and rifampin (a strong CYP3A inducer) was adequate to predict the

effect of ritonavir (a strong CYP3A inhibitor) on the PK of maribavir following a single dose administration of maribavir and multiple dose administration of ritonavir in healthy subjects (Table 111).

(4) Can the maribavir PBPK model predict the effect of phenobarbital and efavirenz (moderate CYP3A inducers) on the PK of maribavir following oral administration in healthy subjects?

Yes. The maribavir model validated using clinical data with ketoconazole (a strong CYP3A inhibitor) and rifampin (a strong CYP3A inducer) was adequate to predict the effect of phenobarbital and efavirenz (moderate CYP3A inducers) on the PK of maribavir following a single dose administration of maribavir and multiple dose administration of phenobarbital or efavirenz in healthy subjects (Table 112). In addition, the simulated maribavir exposure changes with moderate CYP3A inducers following administration of 400, 800, or 1,200 mg, BID maribavir as compared to maribavir exposure after dosing of maribavir alone (400 mg BID) is shown in Table 112.

(5) Can the maribavir PBPK model predict the effect of carbamazepine and phenytoin (strong CYP3A inducers) on the PK of maribavir following oral administration in healthy subjects?

Yes. The maribavir model validated using clinical data with ketoconazole (a strong CYP3A inhibitor) and rifampin (a strong CYP3A inducer) was adequate to predict the effect of carbamazepine and phenytoin (strong CYP3A inducers) on the PK of maribavir following a single dose administration of maribavir and multiple dose administration of carbamazepine or phenytoin in healthy subjects (Table 112). In addition, the simulated maribavir exposure changes with strong CYP3A inducers following administration of 400, 800 or 1,200 mg, BID maribavir as compared to maribavir exposure after dosing of maribavir alone (400 mg BID) is shown in Table 112.

(6) Can the maribavir PBPK model predict the effect of maribavir on the PK of rosuvastatin (BCRP substrate) following oral administration in healthy subjects?

No, but provided supportive information. The Applicant used the in vitro obtained Ki value (b) (4) μM) and a Ki value ((b) (4) μM) estimated using SIVA 4.0 to assess the effect of maribavir on the PK of rosuvastatin. In addition, the effect of different BCRP phenotypes in subpopulations on the maribavir mediated inhibitory effect on rosuvastatin PK was also evaluated. These modelling efforts showed a positive inhibitory effect of maribavir on the PK of rosuvastatin. Due to the uncertainties regarding the in vitro to in vivo extrapolation of the Ki values of BCRP inhibitors, the maribavir model was not considered adequate to accurately predict the effect of maribavir on the PK of rosuvastatin. However, the DDI potential of maribavir with rosuvastatin cannot be excluded.

Table 111. Observed and Simulated Maribavir Geometric Mean C_{max} and AUC Ratios in the Presence and Absence of CYP Inhibitors in Healthy Subjects

	Observed		Predicted	
	AUCR	$C_{max}R$/ $C_{trough}R$	AUCR	$C_{max}R$/ $C_{trough}R$
Ketoconazole, 400 mg SD	1.53	1.10	1.53	1.17
Ketoconazole, 400 mg QD			1.46	1.29
Ritonavir, 100 mg BID			1.61	1.36
Diltiazem, 60 mg TID			1.09	1.06
Erythromycin, 500 mg TID			1.43	1.26

Source: Physiologically based pharmacokinetics report N10325M-SHP620.
Abbreviations: AUCR, area under the curve ratio; $C_{max}R$, maximum concentration ratio; $C_{trough}R$, trough concentration ratio; CYP, cytochrome P450; SD, single dose; TID, thrice daily; QD, once daily

Table 112. Predicted Maribavir Exposure at Various Doses With Concomitant Strong or Moderate CYP3A Inducers Compared to Maribavir 400 mg BID Alone

		Maribavir Exposure Ratio (With Versus Without Inducer)[c]		
Parameter	Maribavir	AUCR	$C_{max}R$	$C_{trough}R$[d]
Rifampin 600 mg QD	400 mg BID	0.34	0.54	0.04[a]/0.24[b]
	800 mg BID	0.72	1.10	0.10[a]/0.31[b]
	1,200 mg BID	1.07	1.66	0.14[a]/0.43[b]
Carbamazepine 400 mg QD	400 mg BID	0.70	0.77	0.53[a] /0.54[b]
	800 mg BID	1.40	1.53	1.06[a]/1.07[b]
	1,200 mg BID	2.10	2.30	1.58[a]/1.56[b]
Phenytoin 300 mg QD	400 mg BID	0.57	0.68	0.30[a] /0.40[b]
	800 mg BID	1.13	1.37	0.59[a]/0.69[b]
	1,200 mg BID	1.70	2.05	0.90[a]/1.00[b]
Phenobarbital 100 mg QD	400 mg BID	0.60	0.72	0.31[a]/0.44[b]
	800 mg BID	1.20	1.45	0.62[a]/0.75[b]
	1,200 mg BID	1.80	2.17	0.94[a]/1.02[b]
Efavirenz 600 mg QD	400 mg BID	0.56	0.74	0.21[a]/0.34[b]
	800 mg BID	1.12	1.48	0.41[a]/0.55[b]
	1,200 mg BID	1.68	2.22	0.62[a]/0.76[b]

Sources: AUCR, $C_{max}R$ and $C_{trough}R$ without LLOQ of 0.2 µg/mL applied to the simulated data were from Applicant's physiologically based pharmacokinetics report N10325M-SHP620.
[a] Without LLOQ of 0.2 µg/mL applied to the simulated data.
[b] With LLOQ of 0.2 µg/mL applied to the simulated data.
[c] Geometric mean ratio.
$C_{trough}R$ with LLOQ of 0.2 µg/mL applied to the simulated data was from the FDA reviewer's calculation based on the Applicant's simulations.
Abbreviations: AUCR, area under the curve ratio; BID, twice daily; $C_{max}R$, maximum concentration ratio; $C_{trough}R$, trough concentration ratio; CYP, cytochrome P450; LLOQ, lower limit of quantitation; QD, once daily

15. Trial Design: Additional Information and Assessment

Trial 303

Table 113. Examples of Virologic Responses for the Primary Efficacy Endpoint, Trial 303

Scenario	CMV DNA Weeks on Study					
	Week 6	Week 7	Week 8	Week 9*	Response	Rationale
1	+ / -	-	-	+/-/NA	Yes	2 consecutive '-' at Week 7 and Week 8
2	+ / -	-	+	+/-/NA	No	Not 2 consecutive '-' at Week 7 and Week 8
3	+ / -	+	-	+/-/NA	No	Not 2 consecutive '-' at Week 7 and Week 8
4	+ / -	-	NA	-	Yes	2 consecutive '-' as shown by available data and both '-' at week 7 and week 9 for missing week 8, otherwise nonresponder
5	-	NA	-	+/-/NA	Yes	2 consecutive '-' as shown by available data and both '-' at week 6 and week 8 for missing Week 7, otherwise nonresponder
6	-	NA	NA	-	Yes	2 consecutive '-' as shown by available data at week 6 and week 9 and both '-', otherwise nonresponder

NA = *not available for evaluation of study drug effect*; reason could be not assessable by lab, or starting alternative anti-CMV treatment, withdrawal from study, etc.

*Week 9 data only to be used if Week 8 data are unavailable or missing.

Notes: Scenarios in the table above are provided as examples and may not be all-inclusive of all possibilities.

Only CMV DNA data evaluable for assessment of effect of study drug will be included (ie, prior to the start of alternative anti-CMV treatment if any).

"-" = CMV DNA concentration <LLOQ (<137 IU/mL)

"+" = CMV DNA concentration ≥LLOQ (ie, quantifiable)

Confirmed clearance of plasma CMV DNA (CMV viremia clearance) = 2 consecutive postbaseline assessments of CMV DNA target <LLOQ, separated by at least 5 days.

NA = *not available for evaluation of study drug effect*; reason could be not assessable by lab, or starting alternative anti-CMV treatment, withdrawal from study, etc.

*Week 9 data only to be used if Week 8 data are unavailable or missing.

Notes: Scenarios in the table above are provided as examples and may not be all-inclusive of all possibilities.

Only CMV DNA data evaluable for assessment of effect of study drug will be included (ie, prior to the start of alternative anti-CMV treatment if any).

"-" = CMV DNA concentration <LLOQ (<137 IU/mL)

"+" = CMV DNA concentration ≥LLOQ (ie, quantifiable)

Confirmed clearance of plasma CMV DNA (CMV viremia clearance) = 2 consecutive postbaseline assessments of CMV DNA target <LLOQ, separated by at least 5 days.

Source: Table 3 in the Statistical Analysis Plan for Investigational New Drug 51001 SDN 486.
Abbreviations: CMV, cytomegalovirus; IU, international units; LLOQ, lower limit of quantitation; NA, not applicable

Table 114. Examples of Virologic Responses for the Key Secondary Efficacy Endpoint, Trial 303

Response (both virological response and symptomatic CMV infection control) at Study Week 8	CMV DNA Assessment Week							Key secondary endpoint responder*	Rationale
	9	10	11	12	14	16	18[1]		
Yes	+/-	+/-	+/-	+/-	+/-	-	+/-/NA	Yes	Data available through week 16, week 16 is "-" and no 2 consecutive "+"during FU
Yes	+/-	+/-	+/-	+/-	+/-	+	+/NA	No	Data available through week 16, week 16 is '+' and Week 18 is "+" or "NA"
Yes	+/-	+/-	+/-	+/-	+/-	+	-	Yes	Data available through week 16, week 16 is '+' but not meeting 2 consecutive "+" criteria based on Week 18 data
Yes	+/-	+/-	+/-	+/-	+/-	+/-	+/-/NA	No	any 2 consecutive '+' in FU
Yes	+/-	+/-	+	-	-	NA	-	Yes	Data available through week 14, no 2 consecutive '+' prior to missing at week 16
Yes	+/-	+/-	+	-	-	NA	+/NA	No	Data available through week 14, no 2 consecutive '+', 2 consecutive '-' prior to missing at week 16
Yes	+/-/NA	+/-/NA	+/-/NA	+/-/NA	NA	NA	+/-/NA	No	Lack of data at both week 14 and 16 to show maintaining effect through week 16
No								No	

[1]Week 18 data will be used only if Week 16 data are unavailable or missing.
*Must also meet the criterion of CMV infection symptom control to be a responder.
NA=not available for evaluation of study drug effect; reason could be starting alternative anti-CMV treatment, withdrawal from study, etc.
"-" = CMV DNA concentration <LLOQ (<137 IU/mL)
"+" = CMV DNA concentration ≥LLOQ (ie, quantifiable)
Notes: Scenarios in the table above are provided as examples and may not be all-inclusive of all possibilities.
Only CMV viremia data prior to receiving nonstudy CMV treatment or rescue treatment will be included in the assessment.
Source: Table 6 in the Statistical Analysis Plan for Investigational New Drug 51001 SDN 486.
Abbreviations: CMV, cytomegalovirus; FU, follow-up; IU, international units; LLOQ, lower limit of quantitation; NA, not applicable

A subject who failed to achieve response for the primary efficacy endpoint was defined to be a non-responder for the key secondary efficacy endpoint. It is noted that plasma CMV DNA assessment done after the start of alternative anti-CMV treatment were not evaluable for the responder assessment toward the study assigned treatment. Responder categorization for maintenance through Week 16 was also summarized in Table 115.

Table 115. Response Categorization for Key Secondary Endpoint

Data at Week 16	Key secondary endpoint responder*
Available, or missing but adjacent data are available	Yes/no based on no 2 consecutive "+"during FU (see Table 6)
Not evaluable or missing due to rescue or alternative anti-CMV treatment	No
Missing with or without CMV viremia clearance maintained at time of discontinuation	No

*Must first be a responder at the end of Study Week 8 with viremia clearance and symptom control, and also meet the criterion of CMV infection symptom control to be a responder.

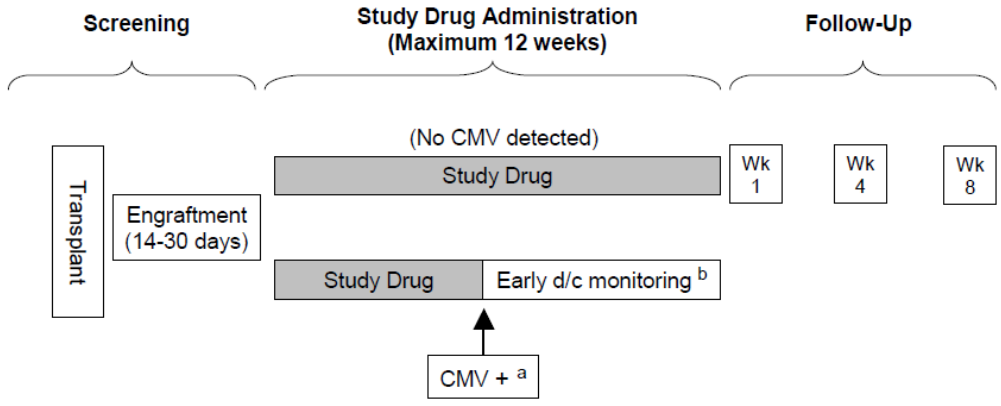
Source: Table 7 in the Statistical Analysis Plan for Investigational New Drug 51001 SDN 486.
Abbreviations: CMV, cytomegalovirus; FU, follow-up

16. Efficacy: Additional Information and Assessment

Maribavir Prophylaxis Trials

Maribavir Trial 1263-200 was a randomized, double-blind, placebo-controlled, dose-ranging Phase 2 study to assess the safety, tolerability, and prophylactic anti-cytomegalovirus activity of maribavir in recipients of allogenic stem cell transplants. The primary efficacy endpoint was the incidence of CMV infection or disease within 100 days post-transplant. Odds ratios and p-values were obtained using the Cochran-Mantel-Haenszel test, adjusting for transplant type (myeloblative or non-myeloblative). See Figure 32.

Figure 32. Study Design Schematic, Trial 200



d/c=discontinuation

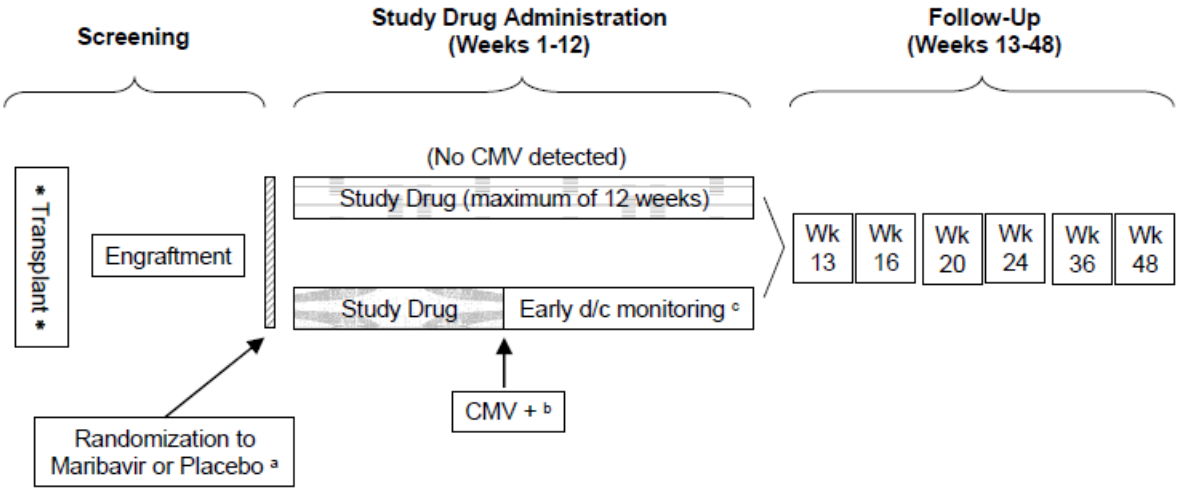
[a] Upon detection of CMV infection (i.e., reactivation) or CMV disease, the subject was managed according to standard CMV treatment practices at the transplant center.

[b] If study drug was discontinued ≤8 weeks into therapy, early d/c monitoring continued weekly through the remainder of the intended 12-week administration period. If study drug was discontinued >8 weeks into therapy, early d/c monitoring continued weekly for 4 weeks.

Source: Figure 1 in the Clinical Study Report.
Abbreviations: CMV, cytomegalovirus; d/c, discontinuation; Wk, week

Maribavir Trial 1263-300 was a randomized, double-blind, placebo-controlled Phase 3 study to assess the efficacy and safety of prophylactic use of maribavir for the prevention of cytomegalovirus disease in recipients of allogenic stem cell transplants. The primary endpoint was the incidence of Endpoint Committee-confirmed CMV disease within 6-months post-transplant. Odds ratios and p-values were obtained using the Cochran-Mantel-Haenszel test, adjusting for recipient CMV serostatus (recipient positive or negative) and transplant type (myeloblative or non-myeloblative/reduced intensity). See Figure 33.

Figure 33. Study Design Schematic, Trial 300



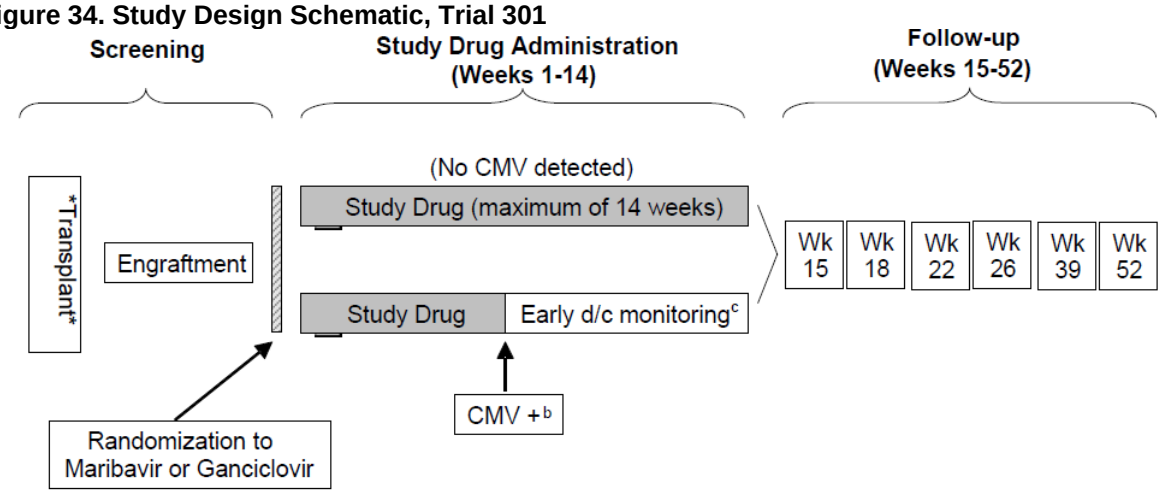
d/c=discontinuation

a: Dosing with study drug commenced between 14 and 30 days post-transplant (inclusive).
b: Upon detection of CMV infection or CMV disease, subjects were managed according to standard CMV treatment practices at the transplant center.
c: If study drug was discontinued prematurely, early d/c monitoring continued weekly through the remainder of the intended 12-week administration period.

Source: Figure 1 in the Clinical Study Report.
Abbreviations: CMV, cytomegalovirus; d/c, discontinuation; Wk, week

Maribavir Trial 1263-301 was a randomized, double-blind Phase 3 study to assess the efficacy and safety of prophylactic use of maribavir versus oral ganciclovir for the prevention of cytomegalovirus disease in recipients of orthotopic liver transplants. The primary endpoint was the incidence of Endpoint Committee-confirmed CMV disease (either symptomatic CMV infection or CMV organ disease) within 6-months post-transplant. The main analysis of the primary endpoint was to determine the non-inferiority of maribavir 100 mg BID compared to ganciclovir 1,000 mg TID using a 95% CI for the event (CMV disease) risk difference between therapy groups (maribavir versus ganciclovir); the non-inferiority assumption was met if the upper limit of the CI was <0.05. P-values were obtained using the Cochran-Mantel-Haenszel test, adjusting for recipient of induction antilymphocyte antibodies (ALA) and geographic region (United States or Europe). See Figure 34.

Figure 34. Study Design Schematic, Trial 301



d/c=discontinuation

a: Dosing with study drug commenced within 10 days post-transplant.
b: Upon detection of symptomatic CMV infection or CMV organ disease, subjects were managed according to standard CMV treatment practices at the transplant center.
c: If study drug was discontinued prematurely, early d/c monitoring was to continue weekly through the remainder of the intended 14-week administration period.

Source: Figure 1 in the Clinical Study Report.
Abbreviations: CMV, cytomegalovirus; d/c, discontinuation; Wk, week

After adjusting for multiple dose comparisons against placebo, statistically significant differences were observed in 1263-200 in favor of maribavir compared to placebo for CMV infection or disease with infection assessed by plasma DNA polymerase chain reaction (PCR) assay and initiation of by anti-CMV therapy for the 100 mg BID dose, by plasma DNA PCR assay for the 400 mg QD dose and initiation of anti-CMV therapy for the 400 mg BID dose. See Table 116.

Table 116. Efficacy Results for Study 200

Incidence of CMV Infection or Disease – Within 100 Days Post-transplant				
		Maribavir Dose Group		
	Placebo	100 mg BID	400 mg QD	400 mg BID
ITT population, N	28	28	28	27
ITT evaluable,[a] N	28	27	27	26
CMV infection or disease				
w/infection assessed by pp65 antigenemia assay	11 (39%)	4 (15%) p=0.046	5 (19%) p=0.116	4 (15%) p=0.053
w/infection assessed by plasma DNA PCR assay	13 (46%)	2 (7%) p=0.001	3 (11%) p=0.007	5 (19%) p=0.038
w/infection assessed by initiation of anti-CMV therapy	16 (57%)	4 (15%) p=0.001	8 (30%) p=0.051	4 (15%) p=0.002
CMV disease only	3 (11%)	0 p=0.089	0 p=0.084	0 p=0.091

[a] ITT evaluable excludes subjects who received <7 days of drug due to withdrawal from study or death, and had no virology data after the start of study drug.

NOTE: p-value is from the Cochran-Mantel-Haenszel test stratified by transplant type (myeloablative or non-myeloablative) comparing individual treatment groups to placebo.

Source: Efficacy results in the study synopsis in the Clinical Study Report.
The intent-to-treat (ITT) population was all randomized subjects.
Abbreviations: BID, twice daily; CMV, cytomegalovirus; DNA, deoxyribose nucleic acid; ITT, intent-to-treat; PCR, polymerase chain reaction; QD, once daily

In the primary efficacy analysis for study 1263-300, 4.8% (11 of 227) of subjects in the placebo group and 4.4% (20 of 454) of subjects in the maribavir 100 mg BID group were observed to have incidence of CMV infection or disease within 100 days post-transplant (odds ratio =0.902, p=0.789). See Table 117.

Table 117. Efficacy Results for Study 300

Incidence of CMV Infection or Disease: ITT Population									
	Post-transplant:								
Assessment Period:	100 Days			6 Months			12 Months		
	PBO	MBV	P-value	PBO	MBV	P-value	PBO	MBV	P-value
ITT Population, N:	227	454		227	454		227	454	
CMV Disease:									
EC-confirmed disease	6 (3%)	11 (2%)	0.860	11 (5%)	20 (4%)	0.789	13 (6%)	22 (5%)	0.617
Investigator-determined disease	6 (3%)	16 (4%)	0.542	11 (5%)	26 (6%)	0.637	13 (6%)	28 (6%)	0.825
CMV Infection or EC-confirmed Disease; Infection Assessed by (Central or Local Labs):									
pp65 antigenemia assay	79 (35%)	120 (26%)	0.022	88 (39%)	143 (31%)	0.056	--	--	--
CMV DNA PCR assay	69 (30%)	126 (28%)	0.468	77 (34%)	152 (33%)	0.904	--	--	--
pp65 antigenemia assay or CMV DNA PCR assay	92 (41%)	157 (35%)	0.125	101 (44%)	183 (40%)	0.289	--	--	--
Initiation of anti-CMV therapy	85 (37%)	139 (31%)	0.069	92 (41%)	172 (38%)	0.493	--	--	--

PBO=placebo; MBV=maribavir 100 mg BID; --=not assessed

NOTE: p-value is from the Cochran-Mantel-Haenszel test, adjusting for recipient CMV serostatus (R+ or R-) and transplant type (myeloablative or non-myeloablative/reduced intensity).

Source: Efficacy results in the study synopsis in the Clinical Study Report.
Abbreviations: BID, twice daily; CMV, cytomegalovirus; EC, ITT, intent-to-treat; PCR, polymerase chain reaction

In the primary efficacy analysis, 8% (10 of 120) of subjects in the ganciclovir 1,000 mg TID group and 12% (14 of 113) of subjects in the maribavir 100 mg BID group were observed to have incidence of CMV infection or disease six months post-transplant; the risk difference was 4.1% in favor of oral ganciclovir, 95% CI: -3.8%, +11.9%. Ganciclovir was observed to be superior to maribavir for CMV infection or Endpoint Committee-confirmed disease with infection assessed by central or local labs for the pp65 antigenemia assay, the CMV DNA PCR assay and for the pp65 antigenemia or CMV DNA PCR assay. Although there was no statistically significant difference between the two treatment arms for the last endpoint, a higher percentage of maribavir subjects than ganciclovir subjects initiated anti-CMV therapy. See Table 118.

Table 118. Efficacy Results for Study 301

Incidence of CMV Infection or Disease: ITT-M Population						
Assessment Period:	**100 Days Post-Transplant**			**6 Months Post-Transplant**		
	Ganciclovir 1000 mg TID	**Maribavir 100 mg BID**		**Ganciclovir 1000 mg TID**	**Maribavir 100 mg BID**	
ITT-M Population, N:	120	113	**P-value**	120	113	**P-value**
CMV Disease:						
EC-confirmed CMV disease	0	10 (9%)	0.0007	10 (8%)	14 (12%)	0.2754
Investigator-determined CMV disease	3 (3%)	17 (15%)	0.0008	18 (15%)	22 (19%)	0.3742
CMV Infection or EC-confirmed Disease; Infection Assessed By (Central or Local Labs):						
pp65 antigenemia assay	19 (16%)	49 (43%)	<0.0001	49 (41%)	63 (56%)	0.0283
CMV DNA PCR assay	18 (15%)	59 (52%)	<0.0001	52 (43%)	72 (64%)	0.0024
pp65 antigenemia or CMV DNA PCR assay	24 (20%)	68 (60%)	<0.0001	64 (53%)	81 (72%)	0.0053
Initiation of anti-CMV therapy	5 (4%)	37 (33%)	<0.0001	39 (33%)	46 (41%)	0.2339
NOTE: p-value is from the Cochran-Mantel-Haenszel test, adjusting for receipt of induction ALA and geographic region (US or Europe). Time to event curves showed no significant difference between the two therapy groups in time to onset of CMV disease at 6 months post-transplant. Kaplan-Meier estimates indicated a longer time to onset of CMV infection or EC-confirmed disease in the ganciclovir group compsared to the maribavir group for all four infection endpoints through 6 months post-transplant.						

Source: Efficacy Results in Study Synopsis in the Clinical Study Report
The modified ITT (ITT-M) population was defined as all randomized subjects who received at least one dose of study drug and had participated in the study for at least 14 weeks, or had the potential to receive 14 weeks of study drug by Feb 12, 2009 (as defined by randomization on or before Nov 7, 2008).
Abbreviations: BID, twice daily; CMV, cytomegalovirus; ITT, intent-to-treat; PCR, polymerase chain reaction

Maribavir Treatment Trials

The following summary tables and analyses are for Trial 303.

A similar sensitivity analysis of Week 8 Completers also counted subjects with recurrence during the 12-Week follow-up period as non-responders. In this analysis, 30% (n=11) or the 37 subjects in the investigator-assigned treatment (IAT) arm and 35% (n=64) of the 183 subjects on the IAT arm were responders. The risk difference between maribavir and IAT subjects was only 5% and was not statistically significant, although the trend still favored maribavir subjects compared to active controls (Table 119).

Table 119. Confirmed CMV Viremia Clearance in Subjects Who Received 8 Weeks of Study-Assigned Treatment (Randomized Patients)

Number of Week 8 Completers	Maribavir (N=183) n (%)	IAT (N=37) n (%)	p-Value
Number with CMV viremia clearance at Week 8	129 (70%)	22 (59%)	0.24
Number with CMV viremia recurrence after Week 8	65 (36%)	11 (30%)	
Number with CMV viremia clearance at Week 8, no recurrence	64 (35%)	11 (30%)	0.69

Source: Statistics Reviewer's analyses.
Subjects with recurrence during the 12-week follow-up were counted as non-responders.
Abbreviations: CMV, cytomegalovirus; IAT, investigator-assigned treatment; N, number of subjects in study arm; n, number of subjects within each category

Since the trial may have been subject to open-label selection bias by investigators and/or subjects, FDA requested sensitivity analyses that excluded subjects who discontinued early from the trial because they wanted to be on maribavir treatment rather than IAT. There were still statistically significant treatment effects that favored maribavir over IAT after excluding these early discontinuations (Table 120).

Table 120. Confirmed CMV Viremia Clearance Excluding Early Treatment Discontinuations Within 72 Hours or 7, 14, 21, and 28 Days of Initiating Treatment (Randomized Patients)

Subjects Included in Analysis CMV Viremia Clearance Response	IAT (N=117) n (%)	Maribavir 400 mg BID (N=235) n (%)
Subjects on treatment 72 hours after treatment initiation, n	116	233
Responders	28 (24.1)	131 (56.2)
Nonresponders	88 (75.9)	102 (43.8)
Adjusted difference in proportion of responders (95% CI)[a]		33.1 (23.08, 43.12)
p-value: adjusted[a]		<0.001
Subjects on treatment 7 days after treatment initiation, n	113	232
Responders	28 (24.8)	131 (56.5)
Nonresponders	85 (75.2)	101 (43.5)
Adjusted difference in proportion of responders (95% CI)[a]		32.6 (22.47, 42.79)
p-value: adjusted[a]		<0.001
Subjects on treatment 14 days after treatment initiation, n	98	224
Responders	28 (28.6)	131 (58.5)
Nonresponders	70 (71.4)	93 (41.5)
Adjusted difference in proportion of responders (95% CI)[a]		30.8 (19.87, 41.81)
p-value: adjusted[a]		<0.001
Subjects on treatment 21 days after treatment initiation, n	80	217
Responders	27 (33.8)	131 (60.4)
Nonresponders	53 (66.3)	86 (39.6)
Adjusted difference in proportion of responders (95% CI)[a]		27.5 (15.34, 39.75)
p-value: adjusted[a]		<0.001
Subjects on treatment 28 days after treatment initiation, n	65	214
Responders	25 (38.5)	131 (61.2)
Nonresponders	40 (61.5)	83 (38.8)
Adjusted difference in proportion of responders (95% CI)[a]		23.4 (9.90, 36.94)
p-value: adjusted[a]		<0.001

BID=twice daily; CI=confidence interval; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; IAT=investigator-assigned anti-CMV treatment; N=number of subjects

[a] Cochran-Mantel-Haenszel weighted average approach was used for the adjusted difference in proportion (maribavir – IAT), the corresponding 95% CI, and the p-value after adjusting for the transplant type and baseline plasma CMV DNA concentration, as homogeneity was met.

Percentages were based on the number of randomized subjects who remained on treatment after the designated time period of starting the study-assigned treatment in the randomized set. Subjects with confirmed CMV viremia clearance at the end of Week 8 were considered as responders regardless of whether the study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy. Plasma CMV DNA assessments after starting alternative anti-CMV treatment or rescue treatment were not evaluable for the assessment of study-assigned treatment effect.

Randomized subjects with no efficacy data were treated as nonresponders.

Source: Table 25 in the Clinical Study Report.

The main reasons for treatment discontinuation in the subgroup of refractory subjects were adverse events for subjects in the IAT arm and lack of efficacy, adverse events, and deaths in the maribavir arm (Table 121).

Table 121. Reasons for Treatment Discontinuation Among Refractory Subjects

Reason for Discontinuation	Maribavir (N=235) n (%)	IAT (N=117) n (%)
Subjects refractory to CMV treatment	96 (41)	34 (29)
Reason for discontinuing randomized treatment		
Adverse events	9 (4)	15 (13)
Death	6 (3)	0
Lack of efficacy	12 (5)	2 (2)
Lost to follow-up	0	0
Non-compliance with study schedule	2 (1)	0
Withdrawal by subject	1 (<1)	5 (4)
Other	1 (<1)	2 (2)

Source: Statistics Reviewer's analysis.
Abbreviation: CMV, cytomegalovirus; N, number of subjects in treatment arm; n, number of subjects with indicated reason

The number of subjects with CMV recurrence within the first 6 weeks of Trial 203 was very low. Only 2 (5%) of the 34 maribavir subjects randomized to the 800 mg BID dose were observed to have recurrence. None of the subjects in any of the other treatment groups were observed to have recurrence during the first 6 weeks of the study. Note that recurrence may have been low since subjects were to be treated for at least 3 to 6 weeks and as long as 12 weeks if clinically indicated and recurrence was measured in the first 6 weeks while many subjects could still have been receiving treatment. See Table 122.

Table 122. Number of Subjects With CMV Recurrence Within the First 6 Weeks of Trial 1263-203 (ITT-S Population)

	Maribavir 400 mg BID (N=40)	Maribavir 800 mg BID (N=40)	Maribavir 1200 mg BID (N=39)	Maribavir All Doses (N=119)	Valganciclovir 900 mg BID (N=40)
Subjects achieving confirmed undetectable CMV DNA (central lab) [a]	33	34	31	98	28
Subjects with CMV recurrence (central lab), n (%)					
Yes [b]	0	2 (5.0) [f]	0	2 (1.7) [f]	0
No [c]	25 (62.5)	26 (65.0)	25 (64.1)	76 (63.9)	21 (52.5)
Treatment effect estimate by group					
Estimated rate [d]	0.00	0.06	0.00	0.02	0.00
95% CI	(0.00, 0.11)	(0.01, 0.20)	(0.00, 0.11)	(0.00, 0.07)	(0.00, 0.12)
Treatment comparison with control [e]					
Odds ratio	--	NA	--	NA	
95% CI for the odds ratio	--	(NA, NA)	--	(NA, NA)	
p-value	--	0.9474	--	0.9637	

BID=twice daily; CI=confidence interval; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; ITT-S=Intent-to-treat Safety; NA=not applicable

[a] Subjects with at least 2 consecutive undetectable results separated by at least 5 days, including early withdrawn qualified subjects. Note that the number of subjects achieving undetectable CMV DNA within 6 weeks is higher in the recurrence analysis (overall maribavir: 98 subjects; valganciclovir: 28 subjects) compared with the primary analysis (overall maribavir: 92 subjects; valganciclovir: 26 subjects; see Table 20). This is because both undetectable results had to be "on-treatment" in the primary analysis, and only the first undetectable result had to be "on-treatment" in the recurrence analysis (i.e., the second could be during "follow-up"; see Section 7.2.2). Thus, 8 subjects (6 maribavir and 2 valganciclovir) stopped treatment with study drug after their first undetectable result and had a second undetectable result after they were off treatment. These subjects were counted as achieving undetectable CMV DNA in the recurrence analysis, but not in the primary analysis.

[b] Any recurrence within 6 weeks, including early withdrawn subjects who had recurrence before withdrawal from study.

[c] Did not have recurrence within 6 weeks and had data within 6 weeks after confirmation, including early withdrawn subjects who did not have recurrence before withdrawal from study.

[d] Numerator is number of subjects with recurrence; denominator is number of subjects with confirmed undetectable CMV DNA.

[e] Logistic regression model for maribavir vs. valganciclovir (SAS PROC LOGISTIC): y = treatment + baseline plasma CMV DNA + transplant type.

[f] Subjects 20310-11 and 20335-06 also were in the PP Population.

Source: Table 24 of the Clinical Study Report.

In contrast to the first 6 weeks of the trial, much higher rates of recurrence were observed during the entire study participation period which could have been up to 24 weeks (12 weeks of treatment followed by another 12 weeks off treatment). The previous table was only counting recurrence events that occurred in the first 6 weeks when subjects were being treated. Recurrence rates ranged from 10% in the maribavir subjects randomized to receive the 1,200 mg BID dose to 25% in maribavir subjects randomized to receive the 400 mg BID dose. The recurrence rate for all maribavir subjects was 18.5% compared to only 12.5% in valganciclovir subjects. See Table 123.

Table 123. Number of Subjects With CMV Recurrence Within the Study Participation Period of Trial 1263-203 (ITT-S Population)

	Maribavir 400 mg BID (N=40)	Maribavir 800 mg BID (N=40)	Maribavir 1200 mg BID (N=39)	Maribavir All Doses (N=119)	Valganciclovir 900 mg BID (N=40)
Subjects achieving confirmed undetectable CMV DNA (central lab) [a]	33	34	31	98	28
Subjects with CMV recurrence (central lab)					
Yes [b]	10 (25.0)	8 (20.0)	4 (10.3)	22 (18.5)	5 (12.5)
No [c]	23 (57.5)	26 (65.0)	26 (66.7)	75 (63.0)	23 (57.5)
Treatment effect estimate by group					
Estimated rate [d]	0.30	0.24	0.13	0.22	0.18
95% CI	(0.16, 0.49)	(0.11, 0.41)	(0.04, 0.30)	(0.15, 0.32)	(0.06, 0.37)
Treatment comparison with control [e]					
Odds ratio	1.9	1.3	0.6	1.3	
95% CI for the odds ratio	(0.52, 6.80)	(0.33, 4.77)	(0.14, 2.77)	(0.41, 3.86)	
p-value	0.3349	0.7346	0.5301	0.6843	

BID=twice daily; CI=confidence interval; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; ITT-S=Intent-to-treat Safety

[a] Subjects with at least 2 consecutive undetectable results separated by at least 5 days, including early withdrawn qualified subjects.

[b] Any recurrence during the study, including early withdrawn subjects who had recurrence before withdrawal from study.

[c] Did not have recurrence during the study and had data after confirmation, including early withdrawn subjects who did not have recurrence before withdrawal from study.

[d] Numerator is number of subjects with recurrence; denominator is number of subjects with confirmed undetectable CMV DNA.

[e] Logistic regression model for maribavir vs. valganciclovir (SAS PROC LOGISTIC): y = treatment + baseline plasma CMV DNA + transplant type.

Source: Table 25 of the Clinical Study Report.

The use of any non-study systemic anti-CMV therapies after Day 1 and within 6 weeks in the intent-to-treat safety population was comparable in each treatment arm, ranging from 32% in subjects randomized to the 1,200 mg BID dose of maribavir and to valganciclovir to 36% in subjects randomized to the 800 mg BID dose of maribavir. See Table 124.

Table 124. Use of Any Non-Study Systemic Anti-CMV Therapies After Day 1 and Within 6 Weeks (ITT-S Population)

	Maribavir 400 mg BID (N=40)	Maribavir 800 mg BID (N=40)	Maribavir 1200 mg BID (N=39)	Maribavir All Doses (N=119)	Valganciclovir 900 mg BID (N=40)
Use of any non-study systemic anti-CMV therapies					
Yes	7	4	7	18	8
No	33	36	32	101	32
Treatment effect estimate by group					
Estimated rate	0.18	0.10	0.18	0.15	0.20
95% CI	(0.07, 0.33)	(0.03, 0.24)	(0.08, 0.34)	(0.09, 0.23)	(0.09, 0.36)
Treatment comparison with control [a]					
Odds ratio	0.8	0.4	0.8	0.7	
95% CI for the odds ratio	(0.25, 2.88)	(0.11, 1.54)	(0.22, 2.72)	(0.25, 1.72)	
p-value	0.7870	0.1848	0.6975	0.3920	

BID=twice daily; CI=confidence interval; CMV=cytomegalovirus; ITT-S=Intent-to-treat Safety

[a] Logistic regression model for maribavir vs. valganciclovir (SAS PROC LOGISTIC): y = treatment + baseline plasma CMV DNA + transplant type.

Source: Table 26 of the Clinical Study Report.

The Kaplan-Meier estimate of median event time to confirmed undetectable plasma CMV DNA (central laboratory) within 6 weeks in the intent-to-treat safety population was 21 days (95% CI: 15 to 22 days) in all maribavir subjects which was slightly longer than the 17 days (95% CI: 8 to 25 days) for observed for valganciclovir subjects. Kaplan-Meier estimates of the first and third quartiles were similar in both treatment groups (9 and 25 days for maribavir subjects and 8 and 30 days for valganciclovir subjects). See Table 125.

Table 125. Time to Confirmed Undetectable Plasma CMV DNA (Central Laboratory) Within 6 Weeks (ITT-S Population), Trial 203

	Maribavir 400 mg BID (N=40)	Maribavir 800 mg BID (N=40)	Maribavir 1200 mg BID (N=39)	Maribavir All Doses (N=119)	Valganciclovir 900 mg BID (N=40)
Subjects with missing data, n (%) [a]	1 (2.5)	0	1 (2.6)	2 (1.7)	1 (2.5)
Subjects with event, n (%) [b]	31 (79.5)	33 (82.5)	28 (73.7)	92 (78.6)	26 (66.7)
Subjects censored, discontinued, n (%) [b]	1 (2.6)	1 (2.5)	2 (5.3)	4 (3.4)	2 (5.1)
Subjects censored, ongoing, n (%) [b]	7 (17.9)	6 (15.0)	8 (21.1)	21 (17.9)	11 (28.2)
Median observed event time (days) [c]	15.0	22.0	15.0	15.0	8.5
Kaplan-Meier estimate (days) [d]					
1st quartile	9.0	14.0	9.0	9.0	8.0
Median (95% CI)	15.0 (15.0, 22.0)	22.0 (16.0, 29.0)	21.0 (14.0, 22.0)	21.0 (15.0, 22.0)	17.0 (8.0, 25.0)
3rd quartile	25.0	29.0	29.0	29.0	30.0
Treatment comparison with control					
Cox model analysis [e]					
Hazard ratio	1.01	1.44	1.14	1.17	
95% CI	(0.58, 1.75)	(0.83, 2.49)	(0.65, 1.99)	(0.75, 1.83)	
p-value	0.9687	0.1967	0.6516	0.4979	

BID=twice daily; CI=confidence interval; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; ITT-S=Intent-to-treat Safety

[a] No plasma CMV DNA measurement post-baseline within the assessment period (ie, 6 weeks). Percentages are based on the number of subjects in each treatment group (ITT-S Population).

[b] Percentages are based on the number of subjects with a non-missing value in each treatment group (ITT-S Population).

[c] Includes only non-censored times.

[d] Kaplan-Meier estimates for maribavir and valganciclovir (SAS PROC LIFETEST): time × censor = treatment.

[e] Cox proportional hazards regression model for maribavir vs. valganciclovir (SAS PROC PHREG): time × censor = treatment + baseline plasma CMV DNA + transplant type.

Source: Table 28 of the Clinical Study Report.

17. Clinical Safety: Additional Information and Assessment

17.1. Supplementary Safety Information, Trial 303

Table 126 summarizes the 40 subjects with adverse events with fatal outcome.

Table 126. List of AEs Leading to Death, Safety Population, Trial 303

Subject ID	Age (Years)	Sex	Onset Day	Last Dose Day	Study Day of Death	Death Day Relative to Last Dose	Cause of Death (Preferred Term)
Maribavir—AEs leading to death during the on-treatment period							
(b) (6)	35	M	-3	58	94	37	Hodgkin's disease recurrent (this AE started 3 days before initiation of study treatment)
	73	F	47	54	59	6	Acute graft-versus-host disease
	28	M	41	39	104	66	Leukemia recurrent
	63	M	7	12	15	4	Hypoxia
	61	M	48	47	48	2	Cardiac arrest
	31	M	43	40	43	4	Acute lymphocytic leukemia recurrent
	60	M	2	2	3	2	Deep vein thrombosis
	71	F	17	58	94	37	Respiratory failure
	58	F	21	17	54	38	Multiple organ dysfunction syndrome
	65	F	36	54	55	2	CMV colitis
	58	M	7	4	7	4	Drug interaction[a]
	63	F	8 11	8	23	16	CMV syndrome Dyspnea
	43	F	29	29	35	7	General physical health deterioration
	58	F	13	14	15	2	Pulmonary embolism
	60	M	16	17	26	10	Respiratory failure
	69	F	38	56	66	11	Acute myeloid leukemia recurrent
	47	M	22	22	27	6	Septic shock

Subject ID	Age (Years)	Sex	Onset Day	Last Dose Day	Study Day of Death	Death Day Relative to Last Dose	Cause of Death (Preferred Term)
IAT—AEs leading to death during the on-treatment period							
(b) (6)	62	F	15	16	25	10	Leukemia recurrent
	63	F	19	21	63	43	Encephalitis CMV
	63	M	12	16	17	2	Respiratory failure
	67	M	11	13	32	20	Acute respiratory distress syndrome
	21	F	55 61 63	48	73	26	Febrile neutropenia[a] Pneumonia[a] Tuberculosis[a]
	47	M	6	11	13	3	Acute myeloid leukemia recurrent
Maribavir—AEs leading to death during the off-treatment period (more than 7 days after the last dose of assigned treatment)							
(b) (6)	68	F	15	11	25	15	Multiple organ dysfunction syndrome
	39	F	95	57	106	50	Multiple organ dysfunction syndrome
	59	M	91	56	116	61	Respiratory tract infection viral
	55	F	46	11	46	36	Myocardial infarction
	60	F	101	59	177	119	Encephalitis CMV
	37	M	105	56	107	52	Septic shock
	54	M	72	48	77	30	Diffuse large B-cell lymphoma
	66	F	128	57	182	126	Encephalitis CMV
	67	F	95	57	125	69	Respiratory infection
	28	M	97	56	123	68	Venous thrombosis
IAT—AEs leading to death during the off-treatment period (more than 7 days after the last dose of assigned treatment)							
(b) (6)	59	F	38[b]	IAT: 34 Maribavir: 57	106[b]	50	Encephalitis CMV
	46	M	69	56	89	34	Acute respiratory distress syndrome
	50	M	71	55	79	25	Pneumonia fungal
	77	F	16	8	38	31	Pneumonia CMV
	70	F	19	6	172	167	CMV enterocolitis
	68	M	141	17	186	170	Post-transplant proliferative disorder
	54	F	93	30	93	64	Neutropenic sepsis

Source: adae.xpt; Software R; Narratives of deaths.
[a] Treatment-emergent adverse event was considered related to study-assigned treatment.
Subject (b) (6) in the IAT group had fatal TEAEs with onset in both the on-treatment observation period (febrile neutropenia) and the follow-up period >7 days after the last dose of study-assigned treatment (pneumonia and tuberculosis). The Investigator considered the pneumonia and tuberculosis to be due to the febrile neutropenia; therefore, this subject is displayed in this table with subjects who had fatal TEAEs in the on-treatment observation period and is not included in the tally of subjects with fatal AEs more than 7 days after the last dose.
[b] Onset of fatal AE was on Day 3 of rescue therapy; death occurred on Day 69 of rescue therapy.
Abbreviations: AE, adverse event; CMV, cytomegalovirus; F, female; IAT, investigator-assigned treatment; ID, identity; M, male; TEAE, treatment-emergent adverse event

17.1.1. Summary of the Two Subjects in Trial 303 (One in the Maribavir Group and One in the IAT Group) Who Had Fatal AEs Considered by the Investigators Related to Assigned Treatment

Subject (b) (6)*:* This was a 58-year-old male with cystic fibrosis who underwent lung transplantation in (b) (6) and kidney transplantation in (b) (6) The subject received valganciclovir for CMV prophylaxis after kidney transplantation. From (b) (6), to (b) (6), the subject was hospitalized and received treatment with intravenous ganciclovir for CMV syndrome and voriconazole followed by posaconazole for "upper respiratory infection with Aspergillus" and intravenous ganciclovir ((b) (6) to (b) (6)) for CMV syndrome. The subject consented to participate in Trial SHP620-303 and he received the first maribavir dose on (b) (6) (Study Day 1) and was discharged home on Study Day 3 (subject lived alone). CMV DNA levels on Day 1 were 19,122 IU/mL. Study Day 4 was the last day the site had contact with the subject. On Study Day 7 the subject was found dead at home by family members. No autopsy was performed.

The Investigator interpreted this event as sudden cardiac death due to arrhythmia, and reported it as related to maribavir based on the possibility of drug-drug interaction, with posaconazole cited as the agent of concern causing the arrhythmia. However, the Applicant disagreed with Investigator's assessment. Although the Applicant cannot rule out the possibility of cardiac arrhythmia resulting in death, maribavir has not been associated with either QTc prolongation or arrythmia. The Applicant believes that the most likely agents were domperidone (started on (b) (6) for anorexia) and posaconazole. Maribavir does not appear to cause QTc prolongation and does not affect the CYP3A4 at doses up to 1,200 mg. However, domperidone is associated with QTc prolongation. In addition, domperidone is a substrate of CYP3A4 and its use is not recommended with potent CYP3A4 inhibitors like posaconazole.

Reviewer's comment: I agree with Applicant's assessment that in the potential case scenario of cardiac arrhythmia resulting in death, the most likely agent was domperidone with the risk increased with the use of posaconazole.

Subject (b) (6): This was a 21-year-old female with a history of acute myeloid leukemia for which she underwent a myeloablative peripheral blood stem cell transplant on (b) (6). On (b) (6), she experienced CMV viremia. On (b) (6) she consented to participate in Trial SHP620-303 and she was randomized to IAT and she received the first dose of oral valganciclovir. The valganciclovir was withdrawn on Study Day 48 and the subject died on Day 73 due to tuberculosis.

On Study Days 21, 41, and 55 the subject had a low neutrophil counts of 1.0×10^9/L which were reported as an ongoing treatment-emergent AE of neutropenia with onset on Day 34. Valganciclovir was discontinued on Day 48. On Study Day 55, the subject was hospitalized with febrile neutropenia for which she had been treated with antibiotics for approximately 2 months. On Day 61, the subject's respiratory condition deteriorated. A chest computed tomography scan was done showed bilateral pneumonia. She was intubated and mechanically ventilated. However, the subject's clinical condition deteriorated. On Day 63 she was diagnosed with tuberculosis and influenza B. She died on Day 73. An autopsy report was not provided.

CMV DNA levels (IU/mL) for this subject were: Day 1: 8,608, Day 6: 12,920, Day 13: 4,489, Day 20: 1,721, Day 27: 10,036, Day 34: 27,984, Day 41: 64,893, Day 48: 278,076; Day 55: 445,596, Day 62: 518,058.

The Investigator assessed the event of febrile neutropenia as related to valganciclovir and the events of pneumonia and tuberculosis due to febrile neutropenia and thus related to the subject's IAT treatment. The Applicant agreed with the Investigator's assessment.

Reviewer's comment. Agree that valganciclovir may have contributed to neutropenia and subsequently to the events of pneumonia and tuberculosis. However, the underlying disease and immunosuppressive regimens had probably greater impact on subject's complications and outcome than the use of valganciclovir. Additional information is needed to help defining the contribution of valganciclovir to these events. For example, white blood cell counts after the transplantation and before initiating treatment with valganciclovir. Further, white blood cell counts after drug discontinuation would be useful for interpretation of this case.

17.2. Supplementary Safety Information, Trial 202

Table 127. AEs Leading to Death, Safety Population, Trial 202

Subject ID	Age (Years)	Sex	Onset Day	Last Dose Day	Study Day of Death	Death Day Relative to Last Dose	Cause of Death (Preferred Term)
Maribavir 400 mg BID (N=10)							
(b) (6)	53	F	66	66	67	1	Sepsis
	47	F	44	16	49	33	Acute respiratory distress syndrome
	51	F	35	43	58	15	Leukemia recurrent
	40	M	9	8	22	14	Encephalopathy
	59	M	17	27	30	3	Renal impairment
	32	M	16	26	30	4	Multi-organ failure
			27	26	30	4	Sepsis
	58	M	178	171	183	12	Esophageal carcinoma
	61	F	79	62	79	17	Cytomegalovirus infection
	55	F	104	91	104	13	Cardio-respiratory arrest
	64	F	157	157	158	1	Central nervous system hemorrhage
Maribavir 800 mg BID (N=12)							
(b) (6)	61	M	65	72	72	1	Sepsis
	66	M	34	41	41	1	Pneumonia
	63	M	55	54	57	3	Bacteremia
	60	M	67	47	88	40	Myelodysplastic syndrome
	64	M	29	54	66	12	Encephalitis cytomegalovirus
	64	F	9	13	14	1	Pneumonia
	70	M	17	48	54	6	Renal impairment
	57	F	61	64	140	75	Herpes simplex meningoencephalitis
	65	F	12	22	27	5	Post-transplant lymphoproliferative disorder
	68	M	6	7	13	5	Multi-organ failure[a]
	63	F	133	77	135	57	Cerebral hemorrhage
	74	F	103	87	103	15	Acute graft-versus-host disease

Subject ID	Age (Years)	Sex	Onset Day	Last Dose Day	Study Day of Death	Death Day Relative to Last Dose	Cause of Death (Preferred Term)
Maribavir 1,200 mg BID (N=10)							
(b) (6)	29	M	120	77	122	44	Sepsis
	26	M	55	68	89	20	Leukemia recurrent
	42	M	27	49	50	2	Respiratory failure
			50	49	50	2	Acute graft-versus-host disease
			50	49	50	2	Nocardiosis
			50	49	50	2	Renal impairment
	59	M	8	14	14	1	Pneumonia, cytomegaloviral
	38	F	6	22	25	3	Multi-organ failure
	20	M	3	5	14	9	Pneumonia, cytomegaloviral
	59	M	113	83	118	35	Renal impairment
	61	M	9	9	11	2	Sepsis
	50	M	37	39	39	1	Multi-organ failure
	70	M	27	21	34	13	Acute respiratory distress syndrome

Source: adae.xpt; Software R; Narratives of deaths.
[a] Treatment-emergent adverse event was considered related to study-assigned treatment.
Abbreviations: AE, adverse event; BID, twice daily; CMV, cytomegalovirus; F, female; ID, identity; M, male; N, number of subjects who died in indicated study arm; TEAE, treatment-emergent adverse event

17.2.1. Summary of the Subject in Trial 202 Who Had Fatal AE Considered by the Investigator Related to Study-Assigned Treatment

Subject (b) (6): This was a 68-year-old white male with a medical history significant for non-Hodgkin's lymphoma, chronic renal failure, and diabetes mellitus type 1 for which he underwent pancreas transplantation ((b) (6)), and graft pancreatitis. On (b) (6), he was enrolled in Trial 202 and he was assigned to receive maribavir 800 mg twice daily (Study Day 1). The subject experienced angina (Study Day 4), encephalopathy (Study Day 6), and multi-organ failure on Study Day 6 which resulted in subject's death on Study Day 13). Maribavir was discontinued on Study Day 7 because of the serious adverse event of multi-organ failure. Treatment of multi-organ failure included different antibiotics and anti-fungal medications for possible sepsis. However, the subject continued to decline despite treatment efforts, and he expired on Study Day 13. His laboratory results are listed in Table 128.

Table 128. Laboratory Test Results, Trial 202

Parameter (Units)	Normal Range	Baseline	Result	Date
Alanine aminotransferase (U/L)	0-45	36	19	(b) (6)
Albumin (g/L)	32-55	29	28	
Alkaline phosphatase (U/L)	29-149	83	77	
Aspartate aminotransferase (U/L)	0-41	34	30	
Bilirubin (µmol/L)	2-21	14	12	
Blood urea nitrogen (mmol/L)	2.1-8.9	15.0	25.3	
Creatinine (µmol/L)	59-103	103	239	
Hematocrit (ratio)	0.4-0.54	0.26	0.23	
Hemoglobin (g/L)	130-175	88	77	
Leukocytes (thousand/mm^3)	3.5-10.5	2.5	2.2	
Neutrophils (thousand/mm^3)	2.1-7.8	2.1	1.8	
Platelets (thousand/mm^3)	140-370	16	43	
Potassium (mmol/L)	3.5-5.3	3.2	3.4	
Urine bacteria (not reported)	Not reported	Negative	+	
Urine hemoglobin (not reported)	Not reported	++	++	
Urine protein (not reported)	Not reported	Negative	+	

Source: Narrative of death
Platelet count was verified by slide review; abnormal hematology result has been confirmed.

CMV DNA levels (copies/mL) for this subject were:

- (b) (6) 14,400
- (b) (6): 50,500
- (b) (6): 300,000 and 500,000
- (b) (6): 6000
- (b) (6): 3600
- (b) (6): 9500

Both the Investigator and the Applicant assessed the serious adverse event of encephalopathy and multi-organ failure as possibly related to study drug.

Reviewer's comment: The subject had a very complicated medical history and multiple ongoing problems that could have been associated with subject's complications. Although sepsis appears to be a more likely case scenario, the possibility of maribavir cannot be ruled out.

17.3. Supplementary Safety Information, Trial 203

Table 129. AEs Leading to Death, Safety Population, Trial 203

Subject ID	Age (Years)	Sex	Onset Day	Last Dose Day	Study Day of Death	Death Day Relative to Last Dose	Cause of Death (Preferred Term)
Maribavir 400 mg BID (N=2)							
(b) (6)	52	M	49	42	107	65	Multi-organ failure
			104		107		Sepsis
	56	F	6	10	29	19	Thrombotic microangiopathy
Maribavir 800 mg BID (N=1)							
(b) (6)	62	F	107	50	108	58	Acute respiratory distress syndrome
Maribavir 1,200 mg BID (N=3)							
(b) (6)	66	F	36	36	96	60	Acute myeloid leukemia recurrent
	74	F	9	4	12	8	Pneumonia
			10		12		Sepsis
	55	M	39	27	56	29	Respiratory syncytial virus infection
Valganciclovir (N=3)							
(b) (6)	59	F	3	2	14	12	Sepsis
	60	M	43	29	63	34	*Pneumocystis jirovecii* pneumonia
	63	M	45	15	45	30	Multi-organ failure

Source: adae.xpt; Software R; Narratives of deaths.
Abbreviations: AE, adverse event; BID, twice daily; ID, identity; N, number of subjects who died in indicated study arm

18. Mechanism of Action/Drug Resistance: Additional Information and Assessment

18.1. Mechanism of Action

Maribavir was initially identified in a screen to identify compounds that inhibit the pUL97 serine protein kinase of HCMV. Maribavir inhibited wild-type pUL97 protein kinase in a biochemical assay with a half inhibitory concentration of 3nM (study report V9508M-SHP620; (Biron et al. 2002)). In contrast, the half inhibitory concentration of maribavir against the pUL97 kinase with the L397R amino acid substitution from the 2916rA virus was increased 20,000-fold to 60µM, consistent with the maribavir resistance profile (see resistance section below).

To further assess the mechanism of action, the cell culture activity for maribavir, ganciclovir, 1038U90 (reported to inhibit HCMV DNA concatemer maturation), and phosphonoformate (PFA) against HCMV (strain AD169) was determined by evaluating the 72-hour yield reduction of the virus titer and the concatemer maturation of HCMV DNA (study report V9503M-SHP620). Maribavir inhibited both the exponential rate constant of HCMV DNA synthesis and the total viral DNA synthesized at 90 hours post infection with EC_{50} values of 0.89µM and 0.07µM, respectively. All compounds reduced the yield of HCMV over a 72-hour period following infection (EC_{50} value for maribavir was 0.1µM, compared to 0.4µM, 0.03µM, and 30µM for ganciclovir, 1038U90, and PFA, respectively). The concatemer maturation EC_{50} value for maribavir against HCMV DNA was 27µM, compared to >25µM, 0.08µM, and >500µM for ganciclovir, 1038U90, and PFA, respectively. In contrast to 1038U90, maribavir, ganciclovir, and PFA did not inhibit concatemer processing at concentrations at which they showed strong antiviral activity. These results indicate that maribavir inhibits HCMV DNA synthesis but not viral DNA concatemer maturation. As shown below, the inhibition of HCMV DNA synthesis is not direct as implied by the structure.

The activity of maribavir as well as the 5′-mono- and 5′-triphosphate derivatives of maribavir against HCMV DNA polymerase and human polymerase delta were also evaluated in biochemical assays (study report V12131M-TAK-620). Enzyme activity was measured by incorporation of ^{3}H-deoxynucleotide triphosphates (namely deoxyadenosine triphosphate, deoxycytidine triphosphate, deoxyguanosine triphosphate, and deoxythymidine triphosphate) into activated calf thymus DNA. Maribavir and its 5′-mono- and 5′-triphosphate derivatives at 100µM had no significant effect on the incorporation of deoxynucleoside triphosphates.

Of note, the strict species specificity of HCMV makes studying this virus in an animal model challenging. No animal model perfectly duplicates the human infection. Furthermore, there is variation in drug sensitivity of HCMV compared to various animal CMV which also complicates pre-clinical animal model studies (McGregor and Choi 2011).

18.2. Antiviral Activity in Cell Culture

The cell culture antiviral activity of maribavir has been evaluated against HCMV (strain AD169; glycoprotein B [gB] 2 genotype) using various cell lines and assays (Table 130). The EC_{50} value ranged from 0.03 to 2.2µM depending on the cell line and assay endpoint. The cell culture antiviral activity of maribavir has also been evaluated against HCMV clinical isolates **(**study

report V9499-SHP620) (Table 131). The median EC_{50} values were 0.1µM (n=10, range 0.04 to 0.13µM) and 0.28µM (n=10, range 0.12 to 0.97µM) using DNA hybridization and plaque reduction assays, respectively. The antiviral activity of maribavir in a plaque reduction assay was similar for different gB genotypes. The median EC_{50} values were 0.33µM (n=2, range 0.28 to 0.38µM), 0.51µM (n=1), 0.44µM (n=4, range 0.34 to 0.45µM), and 0.35µM (n=1) against gB1, gB2, gB3, and gB4, respectively (Table 132, study report V12150M-TAK-620). The distribution of gB genotypes in the United States population was reported to be 26 to 50%, 18 to 40%, 23 to 28%, and 4 to 8% for gB1, gB2, gB3, and gB4, respectively (Zipeto et al. 1998; Bale et al. 2000).

Table 130. Cell Culture Antiviral Activity of Maribavir Against Laboratory Strain AD169

Study Number	Virus	Cell Line	Assay	MBV EC_{50} value
V9499M-SHP620 (VP 1040)	HCMV strain AD169	MRC-5 lung fibroblasts	DNA hybridization	0.06µM
		Human diploid fibroblasts (embryonic kidney)	DNA hybridization	0.03µM
		Human diploid fibroblasts (foreskin MRHF)	DNA hybridization	0.2µM
		MRC-5 lung fibroblasts	DNA hybridization	0.046µM
			Plaque reduction	0.22 to 2.2µM
			Single cycle yield reduction	0.07 to 0.2µM
V9500M-SHP620 (VP 1041)	HCMV strain AD169	MRC-5 lung fibroblasts	DNA hybridization	0.08µM
	HCMV strain AD169 recombinant (GCV-resistant)			0.03 to 0.2µM
V9503M-SHP620 (VP 1044)	HCMV strain AD169	MRC-5 lung fibroblasts	DNA hybridization	0.07µM
V9511M-SHP620 (VP 1486)	HCMV strain AD169	MRC-5 lung fibroblasts	ELISA	0.07µM
V9510M-SHP620 (VP 1443)	HCMV strain AD169	MRC-5 lung fibroblasts	DNA hybridization	0.1µM
			Yield reduction	0.1µM
	HCMV strain Towne	MRC-5 lung fibroblasts	Yield reduction	0.6µMb
	HCMV strain AD169	MRC-5 lung fibroblasts	Plaque reduction	NR
	HCMV clinical isolates	MRC-5 lung fibroblasts	Plaque reduction	0.31µM

Source: modified from study reports V9499M-SHP620, V9500M-SHP620, V9503M-SHP620, V9511M-SHP620, V9510M-SHP620
Abbreviations: ELISA, enzyme-linked immunosorbent assay; GCV, ganciclovir; HCMV, human cytomegalovirus; MBV, maribavir; MRHF

Table 131. Cell Culture Antiviral Activity of Maribavir Against HCMV Clinical Isolates

	DNA Hybridization Assay (EC_{50} value, µM)		Plaque Reduction Assay (EC_{50} value, µM)	
Virus Strain	**Maribavir**	**Ganciclovir**	**Maribavir**	**Ganciclovir**
AD169	0.04	0.40	0.97	4.30
C8301	0.04	0.25	0.12	1.10
C8501	0.10	1.00	0.34	1.00
C8910	0.12	0.70	0.19	1.40
C9207	0.03	0.15	0.44	6.70
C8303	0.09	0.80	0.54	0.80
C8302	0.10	0.30	0.16	2.70
C8803	0.13	0.70	0.21	3.40
C8912	0.04	0.50	0.21	2.60
C9003	0.12	1.10	0.56	1.00
C9213	0.04	0.40	0.40	7.00

Source: study report V9499-SHP620 pg. 9
Abbreviations: DNA, deoxyribonucleic acid; EC_{50}, 50% effective concentration; HCMV, human cytomegalovirus

Table 132. Cell Culture Antiviral Activity of Maribavir Against HCMV Glycoprotein B Types

Isolate	gB Genotype	EC_{50} value (µM)
7	1	0.28
10	1	0.38
8	2	0.51
1	3	0.44
3	3	0.45
4	3	0.43
6	3	0.34
2	4	0.35
5	Unknown	0.45
9	Unknown	0.53

Source: study report V12150M-TAK-620 pg. 5
Abbreviations: EC_{50}, 50% effective concentration; gB, glycoprotein B; HCMV, human cytomegalovirus

The cell culture antiviral activity of maribavir and its major metabolite, which is the N-dealkylated derivative VP 44469 (32µM), was evaluated against 2 AD169 derived laboratory strains T2211 and T2890 using the secreted alkaline phosphatase (SEAP) yield reduction assays in MRC-5 cells (study report V12150M-TAK-620). In side-by-side assays, VP 44469 was found to have measurable but much weaker antiviral activity than maribavir, with an EC_{50} value more than 100 times higher than that of maribavir for strain T2211, and approximately 12 times higher than maribavir for strain T2890. The current model of maribavir binding to pUL97 postulates that the isopropyl-amino side chain (lacking in VP 44469) is an important component of its pUL97 binding specificity.

18.3. Antiviral Activity in Cell Culture in the Presence of Serum and Serum Proteins

The Applicant did not provide any data with respect to the impact of serum proteins on the cell culture antiviral activity of maribavir. Of note Merck, the Applicant of letermovir, included maribavir in their study (reviewed in NDA 209939 SDN 000). Normal human dermal fibroblasts were infected with HCMV AD169-tagged with green fluorescent protein at multiplicity of infection of 0.1, treated with maribavir in the presence or the absence of human serum (range from 5 to 40%) or individual human serum proteins, which are the major proteins involved the

binding of drugs (human serum albumin, 45 mg/ml; α-1-acid glycoprotein, 1 mg/ml), and the corresponding EC_{50} values were determined using fluorescence reduction of green fluorescent protein units at 7 days after inoculation using a charge coupled-device camera fluorescence detector. The maribavir EC_{50} value increased ~3-fold in the presence of 40% human serum or α-1-acid glycoprotein. Human serum albumin did not affect the maribavir EC_{50} value.

18.4. Cytotoxicity/Therapeutic Index

The cytotoxicity of maribavir and the positive control zidovudine, were assessed in human bone marrow progenitor cells (study report V9528M-SHP620). The assay assessed toxicity by evaluating growth inhibition in 2 cell colony types (colony-forming units of granulocytes-macrophages and burst-forming units-erythroid) following a 12- to 13-day incubation period. Maribavir had a 50% cytotoxicity concentration of 90μM and 88μM for colony-forming units of granulocytes-macrophages and burst-forming units-erythroid, respectively. In contrast, zidovudine had a 50% cytotoxicity concentration of 8μM and 0.4μM for colony-forming units of granulocytes-macrophages and burst-forming units-erythroid, respectively. Growth inhibition studies to investigate the effects of maribavir (1.5 to 200μM) exposed for 5 days on rapidly dividing cells were also conducted in 3 human T-cell leukemia lines (MOLT-4, CEM, and CEM-$CD4^+$) and 1 human B-cell leukemia line (IM9) (study report V9529M-SHP620) (note: ideally the cells should have been exposed for longer than 5 days). The 50% cytotoxicity concentration was 35μM, 44μM, 76μM, and 43μM for MOLT-4, CEM, and CEM-$CD4^+$ and IM9 cells, respectively. The Applicant did not evaluate the cytotoxicity of maribavir in any of the cell lines that were used for the cell culture antiviral activity studies. However, it appears maribavir is not cytotoxic at concentrations which inhibit HCMV replication in cell culture. The Applicant also did not provide any mitochondrial toxicity data.

18.5. Combination Antiviral Activity in Cell Culture

Maribavir with Approved Drugs for HCMV

Maribavir in combination with cidofovir, ganciclovir, GW275175X (ribopyranoside benzimidazole), foscarnet, letermovir, and the mTOR inhibitor rapamycin was evaluated in checkerboard cell culture assay (Table 133, study report A8644O-SHP620). The combination of maribavir and ganciclovir at the drugs EC_{50} values was antagonistic. This result was anticipated given that ganciclovir needs to initially be phosphorylated by pUL97 for its antiviral activity which would be inhibited by maribavir. Maribavir in combination with cidofovir, GW275175X, foscarnet, letermovir, and rapamycin was not antagonistic at the drugs EC_{50} values. Of note, these data are highlighted in the proposed label.

Table 133. Combination of Maribavir With Approved HCMV Therapies

Drug A	Max[a]	EC_{50} Value[b]	Drug B	Max[a]	EC_{50} Value[b]	HCMV Strain	Synergism Volume μM^2% (95% CI) Synergism	Antagonism	Interpretation
Cidofovir	1µM	0.31	Maribavir	0.8	0.10	4198	0	-28	Not antagonistic
Ganciclovir	32µM	2.0		1.0	0.11	4175	0	-343	Antagonistic
GW275175X	4µM	0.67		0.6	0.12	4190	0	-36	Not antagonistic
Foscarnet	200µM	30		0.8	0.09	4198	0	-41	Not antagonistic
Letermovir	12nM	2.2		0.6	0.12	4200	0	-44	Not antagonistic
Rapamycin	8nM	1.5		0.6	0.11	4175	258	0	Not antagonistic

Source: study report A8644O-SHP620 pg. 17
[a] Maximum concentration and six-fold dilutions of this concentrations were tested in checkboard assays.
[b] Mean EC_{50} value for the individual drug, concentration units same as in the Max column.
Abbreviations: CI, confidence interval; EC_{50}, 50% effective concentration; HCMV, human cytomegalovirus; max, maximum

Combination of Maribavir and Anti-HIV Drugs

The anti-HIV activities of azidothymidine, dideoxycytidine, dideoxyinosine didanosine, indinavir, and lamivudine in combination with maribavir were evaluated (study report V9506M-SHP620). The Applicant found that the anti-HIV drugs do not affect the antiviral activity of maribavir against HCMV and that maribavir did not affect the activities of the anti-HIV drugs. Of note, the Applicant conducted this study in 1998. As such, the HIV drugs chosen are outdated.

18.6. Resistance Development in Cell Culture and Reported in Previous Clinical Studies

The Applicant has not conducted any independent cell culture resistance selection studies. Instead, they have summarized the available resistance data in the literature for maribavir where academic investigators ((b) (4)) have conducted cell culture selection studies. Amino acid substitutions pUL97 L337M, V353A, L397R, T409M, and H411L/N/Y have been selected by maribavir in cell culture (Chou et al. 2007a; Chou and Marousek 2008; Chou et al. 2012; Chou et al. 2013; Chou et al. 2019) and pUL97 F342Y, T409M, H411L/N/Y, and C480F have been observed as treatment-emergent RAS in subjects who were considered clinical failures on maribavir therapy (Table 134). The reductions in susceptibility for these maribavir RAS ranged from 3.4-fold to >200-fold. Furthermore, HCMV carrying the substitutions that confer reduced susceptibility to maribavir do not affect the growth of recombinant HCMV in cell culture, indicating that these pUL97 substitutions do not significantly impact the fitness of virus (Chou et al. 2020). The pUL97 substitutions F342Y and C480F have been observed as treatment-emergent RAS in the current Applicant's clinical studies, but enrichment by valganciclovir/ganciclovir cannot be ruled out (i.e., not detected at baseline due to levels being too low) given that these substitutions were observed only in subjects who had previously been treated with valganciclovir/ganciclovir.

Resistance to maribavir can also occur as a result of amino acid substitutions in pUL27. pUL27 E22stop, W153R, L193F, C218del, R233S, A269T, 301 to 311del, L335P, V353E, W362R,

W362stop, L426F, and the combination of A406V and C415stop were selected in cell culture (Table 135). The reductions in susceptibility for these range from 1.7-fold to 23-fold. HCMV carrying pUL27 substitutions that decreased susceptibility to maribavir do not affect the growth of recombinant HCMV in cell culture, indicating that these substitutions do not significantly impact the fitness of virus (Chou 2009). Additionally, resistant virus with amino acid substitutions in both pUL27 and pUL97 have been reported (pUL27 R233S + pUL97 S337M, 7.2-fold reduction in susceptibility; pUL27 R233S + pUL97 S353A, 27-fold reduction in susceptibility; (Chou et al. 2007b)).

Table 134. Amino Acid Substitutions in pUL97 That Confer Decreased Susceptibility to Maribavir

pUL97	Origin of Strain	Fold Shift in Susceptibility to Maribavir	Fold Shift in Susceptibility to Ganciclovir	Assays	References
L337M	Lab-derived strain[a]	3.4 to 3.5	1.02	SEAP	(Chou et al. 2012)
F342Y	Clinical isolates	4.5	6.0	SEAP	(Chou et al. 2019)
V353A	Recombinant virus Lab-derived strains[a,b]	10-16	1.0 to 1.5	PRA, SEAP	(Chou et al. 2007a; Chou and Marousek 2008; Chou et al. 2012; Chou et al. 2013)
L397R	Recombinant virus Lab-derived strains[a,c]	>200	1.6	DNA hybridization assay, PRA, SEAP	(Biron et al. 2002; Evers et al. 2004; Drew et al. 2006; Chou et al. 2007a; Chou and Marousek 2008)
T409M	Recombinant virus Lab-derived strain[b]	81	0.9	PRA, SEAP	(Chou et al. 2007a; Chou and Marousek 2008)
H411L	Clinical isolates Lab-derived strain[a]	69	0.7	SEAP	(Chou and Marousek 2008)
H411N	Recombinant virus Lab-derived strain[a]	9	1.0	SEAP	(Chou and Marousek 2008)
H411Y	Recombinant virus Lab-derived strain[a]	12	0.5	SEAP	(Chou and Marousek 2008)
C480F	Clinical isolates	224	2.3	SEAP	(Chou et al. 2020)

Source: Chou et al. 2007a, Chou and Marousek 2008, Chou et al. 2012, Chou et al. 2013, Chou et al. 2019
[a] Exonuclease domain II (D413A) DNA polymerase HCMV mutant, modified from reference strain AD169 to incorporate a secreted alkaline phosphatase (SEAP) reporter gene.
[b] HCMV clinical strain.
[c] AD169 strain.
Abbreviation: DNA, deoxyribonucleic acid; PRA, plaque reduction assay; SEAP, secreted alkaline phosphatase

Table 135. Amino Acid Substitutions in pUL27 That Confer Decreased Susceptibility to Maribavir

pUL27	Origin of Strain	Fold Shift in Susceptibility to MBV	Assays	References
E22stop	Lab-derived strain[a]	2.0	Yield reduction assay, SEAP	(Chou 2009)
W153R	Recombinant virus Lab-derived strain[a]	1.7	Yield reduction assay, SEAP	(Chou 2009)
L193F	Recombinant virus Lab-derived strain[a]	2.6	Yield reduction assay, SEAP	(Chou 2009)
C218del	Recombinant virus Lab-derived strain[b]	2.5	Yield reduction assay, SEAP	(Chou 2009)
R233S	Recombinant virus Lab-derived strains[a]	1.8 to 4.8	Yield reduction assay, SEAP	(Chou et al. 2004; Chou et al. 2012)
A269T	Recombinant virus Lab-derived strain[b]	2.0	Yield reduction assay, SEAP	(Chou 2009)
301-311del	Recombinant virus Lab-derived strain[b]	3.1	Yield reduction assay, SEAP	(Chou 2009)
L335P	Recombinant virus Lab-derived strain[d]	23	Yield reduction assay	(Komazin et al. 2003a; Komazin et al. 2003b)
V353E	Lab-derived strain[a]	2.1	Yield reduction assay, SEAP	(Chou 2009)
W362R	Recombinant virus Lab-derived strain[c]	1.9	Lab-derived strain[c]	(Chou et al. 2004)
W362stop	Lab-derived strain[b]	2.2	Yield reduction assay, SEAP	(Chou 2009)
A406 and C415stop	Lab-derived strain[c]	3.5	Yield reduction assay	(Chou et al. 2004)
L426F	Recombinant virus Lab-derived strain[a]	2.2	Yield reduction assay, SEAP	(Chou 2009)

Source: Chou et al. 2004, Chou 2009, Chou et al. 2012, Komazin et al. 2003a, Komazin et al. 2003b
[a] Exonuclease domain II (D413A) DNA polymerase HCMV mutant, modified from reference strain AD169 to incorporate a secreted alkaline phosphatase (SEAP) reporter gene.
[b] HCMV clinical strain.
[c] AD169 strain.
[d] Laboratory strain resistant to BDCRB (2-bromo-5,6-dichloro-1-β-D-ribofuranosyl benzimidazole).
Abbreviation: MBV, maribavir; SEAP, secreted alkaline phosphatase

18.7. Cross-Resistance

The Applicant has not conducted any independent cell culture cross-resistance studies. Instead, they have summarized the available cross-resistance data in the literature for maribavir. Several pUL97 substitutions selected by valganciclovir/ganciclovir or methylenecyclopropane analogues confer cross-resistance to maribavir. These include pUL97 substitutions F342S/Y, K355del, V356G, D456N, V466G, C480R, P521L, and Y617del, each reducing susceptibility to maribavir >4.5-fold (Table 137); FDA review of literature and additional information from Applicant in SDN 014. This result was mechanistically expected for pUL97 substitutions that severely impair or delete its overall kinase function. Other valganciclovir/ganciclovir resistance pathways have not been evaluated for cross-resistance to maribavir. pUL54 DNA polymerase substitutions conferring resistance to valganciclovir/ganciclovir, foscarnet, or cidofovir remained susceptible to maribavir (Drew et al. 2006). The valganciclovir/ganciclovir pUL97 resistance-associated substitutions that confer cross-resistance to maribavir need to be highlighted in the label.

Substitutions pUL97 F342Y and C480F are maribavir treatment-emergent resistance-associated substitutions that confer >1.5-fold reduced susceptibility to valganciclovir/ganciclovir, a fold reduction that is associated with phenotypic resistance to valganciclovir/ganciclovir. The clinical significance of this cross-resistance to valganciclovir/ganciclovir for these substitutions has not been determined.

Amino acid substitutions conferring reduced susceptibility to maribavir remained susceptible to cidofovir and foscarnet (Drew et al. 2006; Chou and Marousek 2008). Conversely, pUL54 DNA polymerase substitutions resistant to valganciclovir/ganciclovir, foscarnet, or cidofovir remained susceptible to maribavir (Drew et al. 2006). Of note, the fold reduction for the pUL54 A987G differ based on the assay used. This substitution resulted in a 4-fold and 125-fold reduced susceptibility to maribavir and ganciclovir, respectively, using the DNA hybridization assay. However, the combination of pUL97 C592G + pUL54 A987G resulted in only a 0.5-fold and 5-fold reduced susceptibility to maribavir and ganciclovir, respectively, using the SEAP assay. The SEAP assay fold change is consistent with other data in which pUL54 substitutions are not associated with maribavir resistance. The pUL54 A987G is typically reported to confer 5-6 fold reduced susceptibility to ganciclovir using the SEAP or plaque reduction assay (Lurain and Chou 2010). Additionally, there are no reports of any pUL27 maribavir resistance-associated substitutions being evaluated for valganciclovir/ganciclovir, cidofovir, or foscarnet cross-resistance. However, cross-resistance is not expected for pUL27 substitutions based on the different mechanisms of action.

Table 136. Cross-Resistance Between Maribavir and Valganciclovir/Ganciclovir

Strain	Origin of Strain	Fold Shift in Susceptibility to Maribavir	Fold Shift in Susceptibility to Ganciclovir	Assays	References
pUL97					
Valganciclovir/ganciclovir resistance substitutions					
Valganciclovir/ganciclovir resistance-associated substitutions expected to impact maribavir treatment					
F342S	Recombinant virus Lab-derived strain[a] (under cyclopropavir)	18	7.8	SEAP	(Chou et al. 2013)
K355del	pUL97-Deficient strain (site-directed mutagenesis)	304	16	Enzymatic assay, SEAP	(Prichard et al. 2005; Chou et al. 2013)
V356G	Recombinant virus Lab-derived strain[a] (under cyclopropavir)	108	5.5	SEAP	(Chou et al. 2013)
D456N	Lab-derived strain[c] (under methylenecyclopropane analogue)	278	12	SEAP	(Komazin-Meredith et al. 2014)
V466G	Clinical isolates (under ganciclovir)	321	11	SEAP	(Chou et al. 2013)
C480R	Lab-derived strain[c] (under methylenecyclopropane analogue)	243	9	SEAP	(Komazin-Meredith et al. 2014)
P521L	Clinical isolates (under ganciclovir)	428 to 445	17	SEAP	(Chou et al. 2013)
Y617del	Lab-derived strain[c] (under methylenecyclopropane analogue)	372	10	SEAP	(Komazin-Meredith et al. 2014)
Valganciclovir/ganciclovir resistance-associated substitutions not expected to impact maribavir treatment					
M460V	Clinical isolates Lab-derived strain[a]	0.4	5.5 to 7.2	SEAP, DNA hybridization	V9500M-SHP620, (Drew et al. 2006)
H520Q	Clinical isolates Lab-derived strain[a]	1.6	5.2	DNA hybridization	V9500M-SHP620
K359E	Clinical isolates Lab-derived strain[a]	1.2	3.8	SEAP	(Chou et al. 2019)
K359Q	Clinical isolates Lab-derived strain[a]	1.3	3.7	SEAP	(Chou et al. 2019)
C592G	Clinical isolates Lab-derived strain[a]	1.3	3.9	SEAP	(Drew et al. 2006)
A594V	Clinical isolates Lab-derived strain[a]	1.6 to 2.1	5.8 to 10.4	SEAP, DNA hybridization	V9500M-SHP620, (Drew et al. 2006)
L595S	Clinical isolates Lab-derived strain[a]	1.7 to 2.5	5.8 to 8.6	SEAP, DNA hybridization	V9500M-SHP620, (Drew et al. 2006)

Strain	Origin of Strain	Fold Shift in Susceptibility to Maribavir	Fold Shift in Susceptibility to Ganciclovir	Assays	References
Maribavir resistance-associated substitutions					
Maribavir resistance-associated substitutions expected to confer cross-resistance to valganciclovir/ganciclovir					
F342Y	Clinical isolates	4.5	6.0	SEAP	(Chou et al. 2019)
C480F	Clinical isolates	224	2.3	SEAP	(Chou et al. 2019)
Maribavir resistance-associated substitutions not expected to confer cross-resistance to valganciclovir/ganciclovir					
L337M	Lab-derived strain[a]	3.4–3.5	1.02	SEAP	(Chou et al. 2012)
V353A	Recombinant virus Lab-derived strains[a,b]	10-16	1.0–1.5	PRA, SEAP	(Chou et al. 2007a; Chou and Marousek 2008; Chou et al. 2012; Chou et al. 2013)
L397R	Recombinant virus Lab-derived strains[a,c]	>200	1.6	DNA hybridization assay, PRA, SEAP	(Biron et al. 2002; Evers et al. 2004; Drew et al. 2006; Chou et al. 2007a; Chou and Marousek 2008)
T409M	Recombinant virus Lab-derived strain[b]	81	0.9	PRA, SEAP	(Chou et al. 2007a; Chou and Marousek 2008)
H411L	Clinical isolates Lab-derived strain[a]	69	0.7	SEAP	(Chou and Marousek 2008)
H411N	Recombinant virus Lab-derived strain[a]	9	1.0	SEAP	(Chou and Marousek 2008)
H411Y	Recombinant virus Lab-derived strain[a]	12	0.5	SEAP	(Chou and Marousek 2008)

Strain	Origin of Strain	Fold Shift in Susceptibility to Maribavir	Fold Shift in Susceptibility to Ganciclovir	Assays	References
pUL54					
Valganciclovir/ganciclovir resistance substitutions					
N408K	Clinical isolates Lab-derived strain[a]	0.5	5.6	SEAP	(Drew et al. 2006; Chou et al. 2020)
L802M	Clinical isolates Lab-derived strain[a]	0.7	0.7	PRA	V9500M-SHP620
A809V	Clinical isolates Lab-derived strain[a]	0.2-0.4	0.9-2.1		(Drew et al. 2006; Chou et al. 2020)
M844T	Clinical isolates Lab-derived strain[a]	1.2	1.7	PRA	V9500M-SHP620
981-2DEL	Clinical isolates Lab-derived strain[a]	0.5	4.6	SEAP	(Chou et al. 2020)
A987G	Lab-derived strain	4	126	DNA hybridization	V9500M-SHP620
A987G+pUL97 C592G	Clinical isolates Lab-derived strain[a]	0.5	5	SEAP	(Drew et al. 2006; Chou et al. 2020)

Source: Biron et al. 2002, Chou et al. 2007a, Chou et al. 2012, Chou et al. 2013, Chou et al. 2019, Chou et al. 2020, Chou and Marousek 2008; Chou et al. 2012, Drew et al. 2006, Evers et al. 2004, Komazin-Meredith et al. 2014, Prichard et al. 2005, study report V9500M-SHP620 pg. 13
[a] Exonuclease domain II (D413A) DNA polymerase HCMV mutant.
[b] HCMV clinical strain.
[c] AD169 strain.
Abbreviations: DNA, deoxyribonucleic acid; HCMV, human cytomegalovirus; PRA, plaque reduction assay; SEAP, secreted alkaline phosphatase

19. Other Drug Development Considerations: Additional Information and Assessment

19.1.1. Impact of Baseline Valganciclovir/Ganciclovir/Foscarnet/Cidofovir Resistance-Associated Substitutions

The impact of baseline valganciclovir/ganciclovir/cidofovir/foscarnet resistance-associated substitution was evaluated to determine if any of these substitutions are predictive of nonresponse.

In pUL97, valganciclovir/ganciclovir resistance-associated substitutions pUL97 M460I/V, H520Q, C592G, A594P/S/T/V, L595F/S/W, C603W and del597 to 599 were present at baseline (Table 137, FDA analysis). The percentage of subjects meeting the primary endpoint for those subjects with pUL97 A594P/T, L595W, and del597 to 599 substitutions was ≤45% (i.e., >10% lower than the overall efficacy). The reductions in susceptibility to maribavir for these substitutions have not been determined. The other valganciclovir/ganciclovir pUL97 resistance-associated substitutions, i.e., M460I/V, H520Q, C592G, A594S/V, L595F/S, and C603W, did not appear to have a significant impact on the efficacy of maribavir. The reductions in susceptibility to maribavir for these are <2.5 fold, with the exceptions of M460I, L595F, and C603W for which the reductions in susceptibility have not been determined. It should be noted

that the number of subjects for each of the pUL97 A594P/T and L595W substitutions and the del597 to 599 was small and subjects with other amino acids substituted at these positions responded (e.g., pUL97 A594S/V and L595F/S) so no definitive conclusions with respect to the impact of these substitutions on the response to maribavir can be made. The reductions in susceptibility for maribavir treatment-emergent resistance-associated substitutions range from 4.5 to 81. These ranges indicate that the minimum fold-shift associated with treatment failure due to cross-resistance is in the 2.6 to 4.5 fold-change range and may explain the variable response for pUL97 A594P (40%; 2 of 5)/T(33.3%; 1 of 3), L595W (0%; 0 of 2), or del 597 to 599 (0%; 0 of 2). Of note, amongst these paired sequences, 77 and 47 in the maribavir and IAT arms, respectively, had one or more valganciclovir/ganciclovir RAS at baseline.

Of note, three subjects had the pUL97 F342Y substitution at baseline. This substitution has previously been identified in the Applicant's Phase 2 study. Additionally, pUL97 F342S has been identified from a cyclopropavir cell culture selection study which conferred cross-resistance to both valganciclovir/ganciclovir and maribavir (Chou et al. 2013). This codon was not included in any of the genotypic resistance analyses of the valganciclovir/ganciclovir clinical studies nor previously reported. However, these data indicate that substitutions at this codon are not infrequent in valganciclovir/ganciclovir failures (0.9%, 3 of 323). Furthermore, one subject in the maribavir-rescue arm had the pUL97 F342Y substitution prior to maribavir treatment. This subject was treated with valganciclovir/ganciclovir prior to the rescue which may have selected this substitution. This subject also failed the maribavir rescue treatment. The proposed minimum fold-shift associated with treatment failure due to cross-resistance is consistent with the data for the pUL97 F342Y substitution which confers a 4.5-fold reduced susceptibility to maribavir.

Table 137. Primary Endpoint by Baseline Valganciclovir/Ganciclovir Resistance-Associated Substitutions in pUL97

Substitution	Fold Shift in Cell Culture	MBV	IAT	% Identity	Common Amino Acid at this Position	Response Rate for MBV in Subjects With the Common AA
All subjects		55.74% (131 of 235)	23.93% (28 of 117)			
F342Y	***vGCV***/GCV: 6.0 ***MBV: 4.5***	***-***	***0% (0 of 3)***	***100***	***F***	***55.38% (118 of 217)***
K359Q	vGCV/GCV: ~4 MBV: 1.3	-	0% (0 of 2)	100	K	55.38% (118 of 217)
M460I[a]	vGCV/GCV: ~4	84.62% (11 of 13)	16.67% (1 of 6)	100	M	51.28% (100 of 195)
M460V[a]	vGCV/GCV: 5-10 MBV: 0.4	77.78% (7 of 9)	0% (0 of 5)	100	M	51.28% (100 of 195)
H520Q	vGCV/GCV: 5-10 MBV: 1.6	80% (8 of 10)	0% (0 of 5)	100	H	53.14% (110 of 207)
DEL590 to 600	N/A	0% (0 of 1)	-	100	A	55.38% (118 of 217)
C592G	vGCV/GCV: 2 to 3 MBV: 1.3	50% (3 of 6)	-	100	C	54.50% (115 of 211)
DEL592 to 602	N/A	0% (0 of 1)	-	100	C	55.38% (118 of 217)
A594P	vGCV/GCV: ~3	**40% (2 of 5)**	**0% (0 of 1)**	**100**	**A**	**54.01% (101 of 187)**
A594S	vGCV/GCV: 4.2	66.67% (2 of 3)	0% (0 of 2)	100	A	54.01% (101 of 187)
A594T	vGCV/GCV: 2.7	**33.33% (1 of 3)**	**0% (0 of 1)**	**100**	**A**	**54.01% (101 of 187)**
A594V	vGCV/GCV: 8.6 MBV: 1.6 to 2.1	63.16% (12 of 19)	27.78% (5 of 18)	100	A	54.01% (101 of 187)
L595F	vGCV/GCV: ~16	66.67% (2 of 3)	50% (1 of 2)	100	L	55.00% (99 of 180)
L595S	vGCV/GCV: 8.5 MBV: 1.7-2.5	53.13% (17 of 32)	25% (4 of 16)	100	L	55.00% (99 of 180)
L595W	vGCV/GCV: 5.1	**0% (0 of 2)**	**0% (0 of 2)**	**100**	**L**	**55.00% (99 of 180)**
E596D	N/A	0% (0 of 1)	-	100	E	54.63% (118 of 216)

Substitution	Fold Shift in Cell Culture	MBV	IAT	% Identity	Common Amino Acid at this Position	Response Rate for MBV in Subjects With the Common AA
E596G	vGCV/GCV: 2.3	-	0% (0 of 2)	100	E	54.63% (118 of 216)
DEL597 to 599	**N/A**	**0% (0 of 2)**	**-**	**100**	**N**	54.88% (118 of 215)
DEL597 to 602	N/A	0% (0 of 1)	-	100	N	54.63% (118 of 216)
DEL598 to 600	N/A	-	0% (0 of 1)	100	G	54.38% (118 of 217)
DEL599 to 601	N/A	-	0% (0 of 1)	100	K	54.38% (118 of 217)
DEL599 to 602	N/A	100% (1 of 1)	-	100	K	54.17% (117 of 216)
DEL600	N/A	100% (1 of 1)	-	100	L	54.17% (117 of 216)
C603W	vGCV/GCV: 5 to 10	84.62% (11 of 13)	40% (4 of 10)	100	C	52.45% (107 of 204)
C607F	vGCV/GCV: 1.6	0% (0 of 1)	0% (0 of 1)	100	C	54.63% (118 of 216)
C607Y	vGCV/GCV: 12.5	-	0% (0 of 1)	100	C	54.63% (118 of 216)

Source: FDA analysis.
Bold: Primary endpoint in the MBV arm ≤45% and ≥2 subjects.
Bold italics: Cross-resistant to maribavir.
[a] One subject in the MBV arm had M460I/V at baseline.
Abbreviations: AA, amino acid; GCV, ganciclovir; IAT, investigator-assigned treatment; MBV, mar bavir; N/A, not applicable; vGCV, valganciclovir

In the pUL54, substitutions pUL54 T503I and A834P had at least two subjects and the primary endpoint was ≤45% (i.e., >10% lower than the overall efficacy) (Table 138, FDA analysis).

Table 138. Primary Endpoint by Baseline Valganciclovir/Ganciclovir/Foscarnet/Cidofovir Resistance-Associated Substitutions in pUL54

Substitution	Fold Shift in Cell Culture	IAT	MBV	% Identity	Common Amino Acid at this Position	Response Rate for MBV in Subjects With Common AA
Total		23.93% (28 of 117)	55.74% (131 of 235)			
N408D	vGCV/GCV: 4.9 CDV: 5.6 FOS: 1.3	0% (0 of 1)	100% (1 of 1)	100	N	53.74% (115 of 214)
N408K	vGCV/GCV: 5.3 CDV: 5.4 FOS: 1.6 MBV: 0.5	0% (0 of 1)	100% (2 of 2)	100	N	53.74% (115 of 214)
F412L	vGCV/GCV: 4.6 CDV: 9.4 FOS: 1.1	0% (0 of 1)	100% (1 of 1)	100	F	54.17% (117 of 216)
D413E	vGCV/GCV: 4.8 CDV: 4.3 FOS: 0.8	-	100% (1 of 1)	100	D	54.17% (117 of 216)
K493N	vGCV/GCV: 4.1 CDV: 2.0 FOS: 3.3	-	100% (1 of 1)	100	K	54.17% (117 of 216)
L501F	N/A	-	100% (1 of 1)	100	L	53.95% (116 of 215)
L501I	vGCV/GCV: 6-10 CDV: 9 FOS: 1.4	-	100% (1 of 1)	100	L	53.95% (116 of 215)
T503I	**vGCV/GCV: 2.9 CDV: 6.1 FOS: 0.5**	**0% (0 of 4)**	**25% (1 of 4)**	**100**	**T**	**54.72% (116 of 212)**
K513N	vGCV/GCV: 6.0 CDV: 12.5 FOS: 1.1	0% (0 of 2)	100% (2 of 2)	100	K	53.74% (115 of 214)
K513T	vGCV/GCV: 4.9 CDV: 19 FOS: 1.0	-	100% (1 of 1)	100	K	53.74% (115 of 214)

Substitution	Fold Shift in Cell Culture	IAT	MBV	% Identity	Common Amino Acid at this Position	Response Rate for MBV in Subjects With Common AA
L516P	vGCV/GCV: 4.4 CDV: 5.9 FOS: 0.9	-	0% (0 of 1)	100	L	54.63% (118 of 216)
P522A	vGCV/GCV: 3.0 CDV: 4.1 FOS: 3.6	-	66.67% (2 of 3)	100	P	53.59% (112 of 209)
P522S	vGCV/GCV: 3.0 CDV: 3.6 FOS: 1.1	0% (0 of 1)	80% (4 of 5)	100	P	53.59% (112 of 209)
DEL524	N/A	-	100% (1 of 1)	100	C	54.17% (117 of 216)
L545S	vGCV/GCV: 3-7.4 CDV: 9 FOS 1.2	0% (0 of 1)	75% (3 of 4)	100	L	53.99% (115 of 213)
Q578H	vGCV/GCV: 3.3 CDV: 2.3 FOS: 4.5	-	50% (1 of 2)	100	Q	54.42% (117 of 215)
V715M	vGCV/GCV: 1.0 CDV: 1.1 FOS: 55	-	0% (0 of 1)	100	V	54.63% (118 of 216)
E756D	vGCV/GCV: 1.2 CDV: 0.7 FOS: 3.4	-	100% (1 of 1)	100	E	54.17% (117 of 216)
E756K	vGCV/GCV: 3.5 CDV: 8 FOS: 2.2	100% (1 of 1)	-	100	E	54.17% (117 of 216)
L773V	vGCV/GCV: 2.5 CDV: 2.5 FOS: 4.4	-	0% (0 of 1)	100	L	54.63% (118 of 216)
A809V	vGCV/GCV: 2.4 CDV: 1.9 FOS: 3.3 MBV: 0.2-0.4	25% (1 of 4)	0% (0 of 1)	100	A	54.63% (118 of 216)
V812L	vGCV/GCV: 2.5 CDV: 3.2 FOS: 2.9	0% (0 of 1)	100% (1 of 1)	100	V	54.17% (117 of 216)

Substitution	Fold Shift in Cell Culture	IAT	MBV	% Identity	Common Amino Acid at this Position	Response Rate for MBV in Subjects With Common AA
P829S	vGCV/GCV: 2.0 CDV: 1.6 FOS: 1.1	-	0% (0 of 1)	100	P	54.63% (118 of 216)
A834P	**vGCV/GCV: 6.1** **CDV: 3.0** **FOS: 6.4**	**-**	**0% (0 of 2)**	**100**	**A**	**54.88% (118 of 215)**
G841A	vGCV/GCV: 3.2 CDV: 2.6 FOS: 4.3	0% (0 of 2)	100% (1 of 1)	100	G	54.17% (117 of 216)
DEL981-982	vGCV/GCV: 8.3 CDV: 2.8 FOS: 3.6 MBV: 0.5	0% (0 of 1)	100% (2 of 2)	100	D	53.95% (116 of 215)
A987G	vGCV/GCV: 5.3 CDV: 11.3 FOS: 1.2 MBV: 4.0	50% (1 of 2)	100% (1 of 1)	100	A	54.17% (117 of 216)

Source: FDA analysis.
Bold: Primary endpoint in the MBV arm ≤45% and ≥2 subjects
Abbreviations: AA, amino acid; CDV, cidofovir; FOS, foscarnet; GCV, ganciclovir; IAT, investigator-assigned treatment; MBV, maribavir; N/A, not applicable; vGCV, valganciclovir

19.1.2. Sensitivity Analyses—Viral Load Assay Issue

The central laboratory used the FDA-approved COBAS® AmpliPrep/COBAS® TaqMan® (CAP/CTM) CMV Test (Roche 2017). The local laboratories could use any quantitative polymerase chain reaction or comparable quantitative HCMV deoxyribonucleic acid (DNA) test. Randomized subjects had a baseline HCMV viral load performed immediately prior to the start of treatment. HCMV DNA quantification for the baseline and all subsequent on-study samples was performed at the central specialty laboratory using the CAP/CTM assay according to the study schedule of assessments. Upon review of subject baseline viral loads, the Applicant noted that 23% (82 of 352) of randomized subjects had a screening viral load ≥910 IU/mL in 2 consecutive assessments as assessed at the local laboratory but had a baseline central laboratory result <910 IU/mL, and in some cases <LLOQ.

The Applicant's observations are not unexpected. The CAP/CTM CMV test is reported to have a wide linear range, with a limit of detection value of 91 IU/mL, LLOQ value of 137 IU/mL, and an upper limit of quantitation of 9,100,000 IU/mL. Additional assays have subsequently been approved and studies have demonstrated that despite significant advancement in the quantification of HCMV DNA, variability persists. Overall, HCMV viral load values are typically lower using the CAP/CTM CMV test (Hayden et al. 2015). Attempts to understand the basis of these discordant results have found that assay performance may be affected by amplicon sizes (especially <86 base pairs [bp]), use of whole blood rather than plasma, commercial detection reagents, amplification target gene, and numerous other variables (Preiksaitis et al. 2016). Additionally, HCMV DNA detected in plasma is highly fragmented and does not always represent circulating virus (Boom et al. 2002; Tong et al. 2017). The implications of the study described by Preiksaitis are that some of the variability in HCMV DNA levels in plasma, and to a smaller extent in whole blood, may be due to the length of the amplicon used to detect it (Preiksaitis et al. 2016). More recently, it has been noted that viral substitutions may affect assay results. In April 2017, Roche issued an updated method sheet in which they reported that substitutions in the highly conserved regions of the viral genome covered by the test primers and/or probes might lead to under-quantitation of or failure to detect the virus (Roche 2017). Given these concerns, the review team advised the Applicant about the issues with the CAP/CTM on April 1, 2019. To this reviewer's knowledge, the Applicant did not respond to this advice. The Applicant decided to continue using this assay despite the advice.

As the assessment of the primary efficacy endpoint, i.e., HCMV DNA <LLOQ at Week 8, is based on central laboratory results, if unaddressed, it may be problematic to adjudicate the viral load outcomes in some of these subjects. To address the issue of assessing virologic outcomes for this ~20% subset of randomized subjects with qualifying screening HCMV viral load but a baseline viral load <910 IU/mL using CAP/CTM at the central laboratory, the Applicant proposed to retest the baseline samples using the FDA-approved Abbott Realtime CMV assay (Abbot 2017). The FDA-approved Abbott Realtime CMV (Abbott) assay aims to mitigate the risk of not detecting or under-quantifying virus due to substitutions in the regions of the viral genome covered by the primers and/or probes by using two small targets. The Abbott amplicons are in pUL34, 95 bp, and pUL80.5, 105 bp, whereas the CAP/CTM assay uses one large 340 bp amplicon that targets the DNA polymerase (pUL54). Of note, the primers of the CAP/CTM assay do not map to regions previously identified as encoding valganciclovir/ganciclovir resistance-associated substitutions ruling out primer mismatch as an explanation for low values in the CAP/CTM CMV Test. The Abbott assay is reported to have a limit of detection value of

31 IU/mL (for genotypes gB1 to gB4) and LLOQ value of 50 IU/mL is reported to have a limit of detection value of 31 IU/mL (for genotypes gB1 to gB4) and LLOQ value of 50 IU/mL.

As expected, there was greater concordance (<10 fold difference) if the local laboratory also used the CAP/CTM CMV Test (91.8%, 112 of 122) compared to other FDA-approved assays such as the Abbott Realtime CMV assay (77.8%, 21 of 27) and the Qiagen CMV assay (Qiagen 2014) (64%, 16 of 25, Table 139, FDA analysis). Unfortunately, the intra-assay variability for CAP/CTM is not expressed in the package insert. The data on the reproducibility between the CAP/CTM test and the Abbott test or the Qiagen test are also not available. Of note, there are comparison data between the CAP/CTM and the Roche COBAS assay where the overall concordance between the assays was >90% (Roche 2017). In the Applicant's study, there was only a 77.4% (24 of 31) concordance which was lower than what was previously reported. According to the Applicant, the samples used by the local laboratory, i.e., screening, are not always the same samples as those used by the central laboratory (i.e., baseline) which may partially explain these lower results. However, that there was 8% (10 of 122) of subjects with >10 fold difference despite using the same assay and sample is concerning. Also as expected, there was greater concordance if the local laboratory also used plasma samples (81%, 201 of 248) compared to whole blood samples (64%, 64 of 100) for their testing (Table 140, FDA analysis).

Table 139. Concordance Between the Local and Central Laboratory by Assay Type

Local Lab Assay Method	>10-Fold Difference
Abbott Real Time	77.8% (21 of 27)
Altona	57.1% (8 of 14)
Arup	50% (1 of 2)
Biomerieux	52.6% (10 of 19)
CAP/CTM	91.8% (112 of 122)
Cobas	77.4% (24 of 31)
Diagenode	0% (0 of 2)
Focus	68.4% (13 of 19)
Lab Corp	100% (1 of 1)
LDT	73.9% (34 of 46)
Luminex	0% (0 of 1)
Qiagen	64% (16 of 25)
Unknown	64.1% (25 of 39)

Source: FDA analysis.

Table 140. Concordance Between the Local and Central Laboratory by Sample Type

Specimen	>10-Fold Difference
Blood	64% (64 of 100)
Plasma	81% (201 of 248)

Source: FDA analysis.

Amongst the subjects with discordant viral load results, 33% (10 of 30) and 23% (12 of 53) had a valganciclovir/ganciclovir resistance-associated substitution(s) at baseline in the IAT and maribavir treatment arms, respectively (Table 141, FDA analysis), and of these subjects, 20% (2 of 10) and 25% (3 of 12) had a baseline viral load <910 IU/mL in the IAT and maribavir treatment arms, respectively. Amongst the subjects with concordant results, 67% (57 of 85) and 59% (106 of 180) had a valganciclovir/ganciclovir resistance-associated substitution(s) at baseline in the IAT and maribavir treatment arms, respectively, and of these subjects, 5% (3 of 57) and 6% (6 of 106) had a baseline viral load <910 IU/mL in the IAT and maribavir treatment

arms, respectively. Eighty-one percent (154 of 189) of subjects had valganciclovir/ganciclovir resistance-associated substitution(s) at baseline and were appropriately enrolled based on the prespecified inclusion criteria (Table 142, FDA analysis). Therefore, the vast majority of the subjects who had valganciclovir/ganciclovir resistance-associated substitution(s) at baseline had baseline viral load levels that were prespecified in the study.

Table 141. Concordance Between the Local and Central Laboratory by Treatment

	>10-Fold Difference							
	No				Yes			
	Valganciclovir/Ganciclovir Resistance				Valganciclovir/Ganciclovir Resistance			
	N		Y		N		Y	
	Baseline VL <910 IU/mL		Baseline VL <910 IU/mL		Baseline VL <910 IU/mL		Baseline VL <910 IU/mL	
Treatment	No	Yes	No	Yes	No	Yes	No	Yes
MBV	56	18	100	6	15	26	9	3
IAT	21	7	54	3	3	17	8	2

Source: FDA analysis.
Abbreviations: IAT, investigator-assigned treatment; MBV, maribavir; VL, viral load

Table 142. Patients With Known Valganciclovir/Ganciclovir Resistance-Associated Substitutions at Baseline

	Baseline VL <910 IU/mL				
	No			Yes	
	>10-Fold Difference			>10-Fold Difference	
Treatment	Local Lab Data N/A	No	Yes	No	Yes
Maribavir 400 mg BID	2	100	9	6	3
IAT	2	54	8	3	2

Source: FDA analysis.
Abbreviations: BID, twice daily; IU, international unit; N/A, not applicable; VL, viral load

The Applicant conducted additional assessments with respect to viral load and genotypic resistance. Twenty-three percent (82 of 352) of subjects, 25% (29 of 117) in the placebo arm and 23% (53 of 235) in the maribavir arms, respectively, had baseline viral load >910 IU/mL at screening from the local lab and <910 IU/mL at the central lab on or before first dose of study drug. Amongst these 82 subjects, the Applicant has genotyped 50 subject samples and of these, 33% (5 of 15) in the control arm and 26% (9 of 35) and in the maribavir arms had valganciclovir/ganciclovir resistance-associated substitution at baseline.

Of these 82 subjects, the Applicant has retested 62 subject samples using the Abbott Realtime CMV assay (Table 143, FDA analysis). The median difference was ~5.4-fold (range 0.88-fold to 176-fold) lower in the CAP/CTM CMV Test compared to the Abbott Realtime CMV assay. Eighty-five percent (17 of 20) and 71% (30/42) of subjects in the placebo and maribavir treatment arms, respectively, were confirmed to have a baseline viral load >910 IU/mL consistent with the findings at the local lab. Amongst these subjects with available baseline genotypic data, 42% (5 of 12) and 26% (7 of 27) had valganciclovir/ganciclovir resistance-associated substitution at baseline in the control and maribavir treatment arms, respectively.

Of the subjects with a baseline viral load <910 IU/mL using the Abbott test, 5% (1 of 20) and 21% (9 of 42) of subjects in the placebo and maribavir treatment arms, respectively, had a viral load <910 IU/mL but >455 IU/mL. Amongst these subjects, none (0 of 1) and 22% (2 of 9) had a valganciclovir/ganciclovir resistance-associated substitution at baseline in the control and

maribavir treatment arms, respectively. Of note, amongst the remaining 20 subjects, the Applicant apparently has sufficient samples to retest 10 subjects (of whom 6 had >10-fold difference between local and central laboratory) and therefore these should be retested using the Abbott test. Additionally, 83 subjects had >10-fold difference between the local and central laboratory results (Table 144, FDA analysis).

Samples from 14 of these subjects (note: 10 of these subjects had <910 IU/mL at central lab) have not been assessed using the Abbott test and have sufficient samples remaining. In order to have confidence in the data, these samples should also be retested using the Abbott test. Additionally, samples from Week 8 amongst those who achieved the primary endpoint should also be retested using the Abbott test. This sampling should include those who relapsed shortly after end-of-treatment (e.g., at Week 9 or 10) as well as those who did not.

Table 143. Concordance Between the Local and Central Laboratory by Treatment

	Treatment							
	MBV				IAT			
	Assessed Using Abbott				Assessed Using Abbott			
	N		Y		N		Y	
Valganciclovir/Ganciclovir Resistance	Sufficient Volume for Retest		Sufficient Volume for Retest		Sufficient Volume for Retest		Sufficient Volume for Retest	
	No	Yes	No	Yes	No	Yes	No	Yes
No or N/A	3	4	36	1	4	5	15	0
Yes	1	1	7	0	0	0	4	1

Source: FDA analysis.
Abbreviations: IAT, investigator-assigned treatment; MBV, maribavir; N/A, not applicable

Table 144. Patients Who Had >10-Fold Difference Between the Local and Central Laboratories

	>10-Fold Difference															
	No								Yes							
	Treatment								Treatment							
	MBV				IAT				MBV				IAT			
	Assessed Using Abbott				Assessed Using Abbott				Assessed Using Abbott				Assessed Using Abbott			
	No		Yes		No		Yes		No		Yes		No		Yes	
	Sufficient Volume for Retest		Sufficient Volume for Retest		Sufficient Volume for Retest		Sufficient Volume for Retest		Sufficient Volume for Retest		Sufficient Volume for Retest		Sufficient Volume for Retest		Sufficient Volume for Retest	
Valganciclovir/Ganciclovir Resistance	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
No or N/A	5	54	14	1	2	21	5	0	1	18	22	-	4	6	10	-
Yes	5	97	4	0	3	51	2	1	2	7	3	-	1	7	2	-

Source: FDA analysis.
Abbreviations: IAT, investigator-assigned treatment; MBV, maribavir; N/A, not applicable

Given that the Applicant has not submitted all of the quality control data for the comparison between the CAP/CTM and the Abbott's assay, the primary endpoint was reassessed after censoring the 82 subjects who a had baseline viral load >910 IU/mL at screening from the local lab and <910 IU/mL at the central lab on or before first dose of study drug. Maribavir remained superior to IAT in achieving confirmed HCMV DNAemia <LLOQ at the end of Week 8 in transplant recipients with resistant/refractory HCMV infection (with or without resistance) (Table 145, FDA analysis).

Fifty-one point six percent (94 of 182) and 25% (22 of 88) of subjects achieved confirmed HCMV DNAemia <LLOQ at the end of Week 8 in the maribavir and IAT arms, respectively (p<0.0001). While it was disappointing that the Applicant did not address the CAP/CTM assay issue upfront, the overall conclusions apparently were not impacted with respect to the efficacy of maribavir.

Table 145. Primary Endpoint at Week 8 (Minus Central Lab <910 IU/mL Using CAP/CTM)

Variable	MBV	IAT	Δ (%)	95% CI	p-Value
Total	51.6% (94 of 182)	25% (22 of 88)	-26.6	(-37.3, -14.3)	<0.0001
Hematopoietic stem cell transplant (HSCT)	50.8% (32 of 63)	24.1% (7 of 29)	-26.7	(-43.5, -5)	0.016
Allogeneic	51.6% (32 of 62)	24.1% (7 of 29)	-27.5	(-44.4, -5.8)	0.014
Autologous	0% (0 of 1)	-	-	-	-
Donor negative/ recipient negative (D-/R-)	25% (1 of 4)	0% (0 of 1)	-25.0	(-69.9, 56.9)	0.58
Donor negative/ recipient positive (D-/R+)	55.6% (15 of 27)	17.6% (3 of 17)	-37.9	(-58.3, -8.3)	0.013
Donor positive/ recipient negative (D+/R-)	40% (2 of 5)	50% (1 of 2)	10.0	(-44.8, 59.4)	0.81
Donor positive/ recipient positive (D+/R+)	51.9% (14 of 27)	33.3% (3 of 9)	-18.5	(-46, 17.5)	0.34
Solid organ transplant (SOT)	52.1% (62 of 119)	25.4% (15 of 59)	-26.7	(-39.5, -11.4)	0.00072
Heart transplant	20% (2 of 10)	0% (0 of 8)	-20.0	(-51, 15.5)	0.18
Intestine transplant	0% (0 of 1)	-	-	-	-
Intestine, liver, pancreas transplant	100% (1 of 1)	0% (0 of 1)	-100	(-100, 12.2)	0.16
Kidney transplant	58.1% (36 of 62)	33.3% (10 of 30)	-24.7	(-42.9, -3)	0.026
Kidney transplant, liver transplant	-	0% (0 of 1)	-	-	-
Kidney transplant, pancreas transplant	66.7% (2 of 3)	100% (3 of 3)	33.3	(-29.1, 79.2)	0.27
Liver transplant	100% (6 of 6)	-	-	-	-
Lung transplant	42.9% (15 of 35)	12.5% (2 of 16)	-30.4	(-49, -2.5)	0.033
Pancreas transplant	0% (0 of 1)	-	-	-	-
HCMV Serostatus missing	0% (0 of 1)	0% (0 of 1)	0.0	(-79.3, 79.3)	-
Donor negative/ recipient negative (D-/R-)	66.7% (4 of 6)	33.3% (1 of 3)	-33.4	(-69.4, 25.4)	0.34
Donor negative/ recipient positive (D-/R+)	33.3% (1 of 3)	0% (0 of 1)	-33.3	(-79.2, 50.5)	0.5
Donor positive/ recipient negative (D+/R-)	54% (54 of 100)	27.1% (13 of 48)	-26.9	(-41, -9.9)	0.0021
Donor positive/ recipient positive (D+/R+)	33.3% (3 of 9)	16.7% (1 of 6)	-16.6	(-61.6, 43.8)	0.47
HCMV Disease category					
Asymptomatic HCMV infection	52.3% (80 of 153)	26.9% (21 of 78)	-25.4	(-36.9, -12)	0.00024
HCMV Syndrome (SOT subjects only)	37.5% (6 of 16)	0% (0 of 8)	-37.5	(-61.4, 0.1)	0.046
HCMV Tissue invasive disease	61.5% (8 of 13)	50% (1 of 2)	-11.5	(-57.1, 36.6)	0.76
HCMV DNA Viral load category					
High	28.6% (4 of 14)	28.6% (2 of 7)	0.0	(-33.1, 39.3)	1
Intermediate	47.1% (32 of 68)	20% (5 of 25)	-27.1	(-43.2, -4.8)	0.018
Low	58% (58 of 100)	26.8% (15 of 56)	-31.2	(-44.7, -15.1)	0.00018

Source: FDA analysis.
Abbreviations: CAP/CTM, COBAS® AmpliPrep/COBAS® TaqMan® CMV Test; CI, confidence interval; D, donor; HCMV, human cytomegalovirus; HSCT, hematopoietic stem cell transplant; IAT, investigator-assigned treatment; IU, international unit; MBV, maribavir; R, recipient; SOT, solid organ transplant

The Applicant has subsequently retested an additional 54 baseline samples using the Abbott test as was requested by the FDA. These additional samples included those who had >910 IU/mL but <2,000 IU/mL as measured by the TaqMan assay. All of these retested samples had greater values measured by the Abbott test. In all, of the 116 baseline samples, 52 had a 10-fold or higher difference between the screening local lab and the baseline central lab CAP/CTM results. In contrast, 20 of 116 had a 10-fold or higher difference between Abbott and CAP/CTM results and 18 of these samples were <910 IU/mL by CAP/CTM. These results are consistent with the previous report describing the lower sensitivity of the CAP/CTM assay (Preiksaitis et al. 2016).

The Applicant has also retested 40 (n=20 from each arm) Week 8 samples amongst those who achieved the primary endpoint. Amongst these retested samples, 28 (n=13 and n=15 from the maribavir arm and IAT arm, respectively) were <137 IU/mL, which is the LLOQ value of the TaqMan assay. Amongst the remaining samples, 8 samples (n=4 and n=4 from the maribavir arm and IAT arm, respectively) were >137 IU/mL and <200 IU/mL, 2 samples (both from maribavir arm) were >200 IU/mL and <400 IU/mL, and 2 samples (one from each arm) that were >700 IU/mL (note: both samples were from subjects who relapsed shortly after achieving the primary endpoint. These results are consistent with the CAP/CTM assay likely measuring a true viral load response, within the limits of quantification.

19.1.3. Distribution of the Virologic Failures

In the maribavir arm, 36% (84 of 235) of subjects were virologic failures and 9% (20 of 235) failed for other reasons (note: virologic failures were defined as subjects with viral load >LLOQ during the treatment phase and had >3 days of treatment) (Table 146, FDA analysis). By comparison, 44% (51 of 117) of subjects in the IAT arm were virologic failures and 32% (38 of 117) failed for other reasons (e.g., tolerability). These results are consistent with the safety profile for maribavir being generally more favorable than the IAT and that many treatment failures in the IAT arm are due to toxicity issues.

Table 146. Virologic Response in Subjects Who Did Not Meet the Primary Endpoint

Variable	MBV % (n/N)	IAT % (n/N)
Viral load <LLOQ at Week 8	56 (131 of 235)	24 (28 of 117)
Virologic failure (>LLOQ at Week 8)	36 (84 of 235)	44 (51 of 117)
Virologic failure: non-responder	19 (16 of 84)	63 (32 of 51)
Virologic failure: partial responder	15 (13 of 84)	16 (8 of 51)
Virologic failure: rebound	13 (11 of 84)	4 (2 of 51)
Virologic failure: breakthrough	52 (44 of 84)	18 (9 of 51)
Other (e.g., discontinuation)	7 (17 of 235)	30 (35 of 117)
<4-Day treatment	1 (3 of 235)	3 (3 of 117)

Source: FDA analysis.
Abbreviations: IAT, investigator-assigned treatment; LLOQ, lower limit of quantitation; MBV, mar bavir; N, number of subjects in treatment arm; n, number of subjects with indicated response

Forty nine-point-six percent (65 of 131) and 39.3% (11 of 28) of subjects experienced a relapse after meeting the primary endpoint at Week 8 in the maribavir and IAT arms, respectively (Table 147, FDA analysis). Most of the relapse in the maribavir arm occurred during the first 2 weeks off treatment. These data are consistent with the viral decay kinetics data where 8 weeks of treatment did not appear to be sufficient to achieve viral load <LLOQ. Additionally, there appears to be an inverse relationship with the baseline viral load levels and the timing of relapse

where those with higher viral loads generally relapsed earlier (Table 148, FDA analysis). Additionally, there was an inverse relationship with the baseline viral load levels and subjects who did not relapse. Note that the large number of relapses indicates that replicating virus was not cleared when CMV DNA was <LLOQ.

Table 147. Relapse in Subjects Who Met the Primary Endpoint by Timing

Variable	MBV	IAT
Met primary endpoint at Week 8	55.7% (131 of 235)	23.9% (28 of 117)
Relapse post-treatment	49.6% (65 of 131)	39.3% (11 of 28)
Relapse at Week 9	40.0% (26 of 65)	18.2% (2 of 11)
Relapse at Week 10	24.6% (16 of 65)	36.4% (4 of 11)
Relapse at Week 11	20.0% (13 of 65)	36.4% (4 of 11)
Relapse at Week 12	4.6% (3 of 65)	9.1% (1 of 11)
Relapse at Week 14	3% (2 of 65)	0% (0 of 11)
Relapse at Week 16	6.2% (4 of 65)	0% (0 of 11)
Relapse at Week 18	1.5% (1 of 65)	0% (0 of 11)
Relapse through Week 10	64.6% (42 of 65)	54.5% (6 of 11)
Relapse through Week 11	84.6% (55 of 65)	90.9% (10 of 11)
Relapse through Week 12	89.2% (58 of 65)	100% (11 of 11)
Relapse through Week 14	92.3% (60 of 65)	100% (11 of 11)
Relapse through Week 16	98.5% (64 of 65)	100% (11 of 11)
Relapse through Week 18	100% (65 of 65)	100% (11 of 11)

Source: FDA analysis.
Abbreviations: IAT, investigator-assigned treatment; MBV, maribavir

Table 148. Baseline Viral Load in Subjects Who Met the Primary Endpoint but Relapsed

Baseline Viral Load	MBV			IAT	
Category	High	Intermediate	Low	Intermediate	Low
Recurrence at Week 9	2	2	0	15	9
Recurrence at Week 10	1	1	3	2	13
Recurrence at Week 11	0	1	3	4	9
Recurrence at Week 12	1	0	1	0	2
Recurrence at Week 14	0	0	0	2	0
Recurrence at Week 16	0	0	0	0	4
Recurrence at Week 18	0	0	0	0	1
Subjects who did not relapse	2	7	9	21	43

Source: FDA analysis.
Abbreviations: IAT, investigator-assigned treatment; MBV, maribavir

19.1.4. Response in Subjects With a High Viral Load

During the treatment phase, eligible subjects were stratified by transplant type (hematopoietic stem cell transplant and solid organ transplant) and by the most recent screening HCMV DNA viral load (Table 149, FDA Analysis). There appears to be an inverse relationship with the baseline viral load levels and the response rate as well as the timing of relapse.

Table 149. Primary Endpoint at Week 8 by Baseline Viral Load Levels

Baseline Viral Load Levels (IU/mL)	MBV	IAT
≥91,000	28.6% (4 of 14)	28.6% (2 of 7)
≥50,000 and <91,000	33.3% (3 of 9)	20% (1 of 5)
≥20,000 and <50,000	43.5% (10 of 23)	25% (3 of 12)
≥9,100 and <20,000	52.8% (19 of 36)	12.5% (1 of 8)
≥5,000 and <9,100	33.3% (7 of 21)	25% (3 of 12)
≥2,000 and <5,000	61.4% (27 of 44)	17.9% (5 of 28)
<2,000	69.3% (61 of 88)	28.9% (13 of 45)

Source: FDA analysis.
Abbreviations: IAT, investigator-assigned treatment; IU, international unit; MBV, maribavir

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

The clinical investigators, Doctors Blumberg, Florescu, Silveira, Poiré and the Applicant, Takeda Pharmaceuticals U.S.A., Inc., were inspected in support of this application. At the site of Dr. Poiré, it was observed that few non-serious adverse events were not reported. At the site of Dr. Silveira, there were two observations related to treatment documentation and drug accountability. These violations were considered unlikely to affect the efficacy or safety results of the study (Protocol SHP-620-303). Overall, based on the results of these inspections, the studies (Protocols SHP-620-303 and 1263-203) appear to have been conducted adequately, and the clinical data generated from the clinical investigators sites and submitted by the Applicant appear to be reliable in support of this new drug application.

Office of Scientific Investigations Inspection Reports

(1) Site #008, Emily Blumberg, M.D.
3400 Spruce Street
Philadelphia, PA 19104
Inspection dates: June 7 to 10, 2021

At this site for Protocol SHP-620-303, a total of 11 subjects were screened and enrolled, and 4 subjects completed the study. Six subjects discontinued the study, and one subject was transferred to a different study site. The subjects and the reasons for discontinuations were verifiable, i.e., there were no discrepancies between the source records and the line listings submitted by the Applicant for discontinuations.

The inspection reviewed the source records for all enrolled subjects for the following: informed consent, study eligibility, efficacy endpoint data, adverse events, and investigational product received. The other records reviewed included, but were not limited to, electronic case report forms (eCRFs), protocol deviations, concomitant medications, randomization, drug accountability

records, site correspondence with the Applicant/monitor/Institutional Review Board, FDA 1572, and financial disclosure records.

The primary and the key secondary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

(2) Site #006, Diana Florescu, M.D.
985400 Nebraska Medical Center
Omaha, NE 68198-5400
Inspection dates: May 6 to 10, 2021

At this site for Protocol SHP-620-303, 19 subjects were screened, 17 were enrolled, and 16 subjects completed the study. One subject discontinued the study due to a schedule conflict.

The inspection reviewed all 17 enrolled subject records. Source records reviewed included, but were not limited to, the informed consent forms, study inclusion/exclusion, study efficacy endpoint data, adverse events, eCRFs, protocol deviations, concomitant medications, progress notes, study drug accountability, and randomization procedures.

The primary and the key secondary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

(3) Site #003, Fernarda Silveira, M.D.
200 Lothrop Street
Pittsburgh, PA 15213
Inspection dates: June 22 to 25, 28 to 29, and July 1, 2001

At this site for Protocol SHP-620-303, 15 subjects were screened and enrolled, and 11 subjects completed the study. Four subjects discontinued the study for the following reasons: Subject # (b) (6) (IAT group) discontinued due to the adverse event of neutropenic fever. Three subjects discontinued due to lack of efficacy: # (b) (6) in IAT group, # (b) (6) in maribavir 400 mg BID group, and # (b) (6) in maribavir 400 mg BID group. All these discontinuations were verifiable against the data line listings.

The inspection reviewed study records for all 15 screened subjects. Records reviewed included, but were not limited to, informed consent forms, subject eligibility, home health care reports, electronic medical records, efficacy data, adverse events, pharmacy log, concomitant medications, eCRFs, investigational product accountability, randomization, site correspondence, FDA form 1572, financial disclosure, study monitoring report and staff training records.

The primary and the key secondary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events. However, there were two observations for the inspection:

- The site did not maintain adequate records for three of the four subjects randomized to IAT (ganciclovir, valganciclovir, foscarnet, or cidofovir) to show that they received the prescribed doses.
- The site did not maintain adequate records related to subject compliance with maribavir dosing and drug accountability at the individual count level. The records include the number of tablets returned by subjects, but the site did not reconcile the number of tablets returned by subjects with the dosing recorded in the electronic diary to identify discrepancies. There was a note to file in some subject records indicating that they did not complete all the required dosing information in the electronic diary.

Reviewer's comment: These findings regarding treatment documentation and drug accountability are unlikely to have an effect on the efficacy or safety results of the study.

(4) Site #M20315, Xavier Poiré, M.D.
Avenue Hippocrate 10
Hématologie Bruxelles, 1,200
Belgium
Inspection dates: June 6 to 11, 2021

At this site for Protocol 1263-203, 10 subjects were screened and enrolled, and 8 subjects completed the study. Two subjects discontinued the study due to adverse events: Subject # (b) (6) in the valganciclovir group discontinued due to septic shock, and Subject # (b) (6) in maribavir 800 mg BID group discontinued due to liver toxicity. These discontinuations and the adverse events were verifiable against the data line listings.

The inspection reviewed subject study records for all 10 screened subjects. Records reviewed included, but were not limited to, Independent Ethics Committee oversight, informed consent, eligibility, protocol adherence, concomitant medications, test article accountability, adverse events, and the efficacy endpoint data.

The primary efficacy endpoint data were verifiable. All serious adverse events were reported. However, a few adverse events in 6 subjects (all in the maribavir group) were not reported to the Applicant and FDA. These adverse events are shown in Table 150.

Table 150. Adverse Events Not Reported to the Applicant and FDA

Subject	Maribavir Dose	Adverse Events
(b) (6)	800 mg BID	Significant loss of appetite Nausea Headache within 15 minutes of taking the pill
	800 mg BID	Dyspnea
	800 mg BID	Decreased appetite
	1,200 mg BID	Decreased appetite
	1,200 mg BID	Increased fatigue Thrush Headache Loss of appetite
	1,200 mg BID	Worsening anorexia Diarrhea

Source: Clinical Inspection Summary, Office of Scientific Investigations.
Abbreviation: BID, twice daily

Office of Scientific Investigations Reviewer's comment: We recommend that the review division consider adding these adverse events to their assessment of the overall safety of maribavir.

(5) Applicant, Takeda Pharmaceutical Company Limited
55 Hayden Avenue
Lexington, MA 02421
Inspection dates: July 19 to 28, 2021

The Applicant Takeda was inspected in accordance with Compliance Program 7348.810 *Bioresearch Monitoring (BIMO) for Sponsor, CRO, and Monitors*. Activities and records reviewed included, but were not limited to, organizational charts, standard operating procedures,

Investigator selection, monitoring plans, monitoring reports, transfer of responsibilities, correspondence, training records, FDA 1572s, financial disclosure forms, eCRFs, protocol adherence, subject protection and ethical oversight, safety plans, adverse events, data management, primary efficacy endpoint, and investigational product accountability records. No issues of concern were identified.

21. Labeling Summary of Considerations and Key Additional Information

Applicant's proposed labeling for Livtencity, submitted on March 23, 2021, was compared with final agreed upon labeling. This review summarizes the major changes to the United States Prescribing Information and provides a cross reference to other sections of the Integrated Review for additional details and rationale for the labeling changes.

General Changes to Prescribing Information

Highlights and Table of Contents were updated for consistency with changes to the full prescribing information.

1 INDICATIONS AND USAGE

- Indications statement was revised to include pediatric patients (12 years of age and older and weighing at least 35 kg) with post-transplant CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir or foscarnet. See Section II.8.3.
- Indications statement was revised to narrow the indication (to exclude patients withoutresistant or refractory CMV infection and/or disease) and include only adults and pediatric patients (12 years of age and older and weighing at least 35 kg) with post-transplant CMV infection that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir or foscarnet. See Section II.6.3.1.4.

2 DOSAGE AND ADMINISTRATION

2.2 Dosage Adjustment When Coadministered with Anticonvulsants

- This subsection was added to highlight drug interaction and dosage adjustment when LIVTENCITY is coadministered with carbamazepine, phenytoin or phenobarbital. See Section II.5, Section II.8.2.1, and Section 14.4.4.2.

(b) (4)

5 WARNINGS AND PRECAUTIONS

The following two warnings and precautions were added:

5.1 Risk of Reduced Antiviral Activity When Coadministered with Ganciclovir and Valganciclovir

LIVTENCITY may antagonize the antiviral activity of ganciclovir and valganciclovir by inhibiting human CMV pUL97 kinase, which is required for activation/phosphorylation of ganciclovir and valganciclovir. Coadministration of LIVTENCITY with ganciclovir or valganciclovir is not recommended *[see Drug Interactions (7.1) and Microbiology (12.4)]*.

5.2 Virologic Failure During Treatment and Relapse Post-Treatment

Virologic failure due to resistance can occur during and after treatment with LIVTENCITY. Virologic relapse during the posttreatment period usually occurred within 4-8 weeks after treatment discontinuation. Some maribavir pUL97 resistance-associated substitutions confer cross-resistance to ganciclovir and valganciclovir. Monitor CMV DNA levels and check for maribavir resistance if the patient is not responding to treatment or relapses *[see Microbiology (12.4) and Clinical Studies (14.1)]*. See Section I.2.2, Section II.7.7.1, and Section 19.1.3.

5.3 Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

In addition to other warning language regarding drug interactions, the following paragraph was added:

Maribavir is primarily metabolized by CYP3A4. Drugs that are strong inducers of CYP3A4 are expected to decrease maribavir plasma concentrations and may result in reduced virologic response; therefore, coadministration of LIVTENCITY with these drugs is not recommended, except for selected anticonvulsants *[see Dosage and Administration (2.2) and Drug Interactions (7.3)]*. See Section II.8.2.1 and Section 14.4.4.2.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

- The safety presentation was revised to remove (b) (4) The revised presentation compares LIVTENCITY with the entire IAT group.. (b) (4)
- Proposed language regarding (b) (4)
- Description of subjects who experienced serious adverse events for LIVTENCITY and IAT and subjects who discontinued study medication due to adverse event in both arms were added. Selected laboratory abnormalities were added in Table 6 comparing LIVTENCITY arm vs. IAT arm. See Section II.7.6.1.

7 DRUG INTERACTIONS

- Drug interaction with digoxin was changed (b) (4) to use with caution and to monitor serum digoxin concentrations. (b) (4)

- Drug interaction with phenobarbital: recommendation changed [redacted] to 1,200 mg twice daily dosage adjustment. [redacted]

8 USE IN SPECIFIC POPULATIONS

[redacted]

8.4 Pediatric Use

Justification for pediatric indications and dosing recommendation for patients 12 years of age and older and weighing at least 35 kg was added.

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

- Added the following exposure-response description: In dose-ranging studies that evaluated doses of 400 mg twice daily and twice daily doses of two and three times the recommended dose, no exposure-response relationship was observed for viral load or probability of unquantifiable plasma CMV DNA. See Section 14.4.2.

12.3 Pharmacokinetics

- Added PK parameters for DDIs with digoxin and anticonvulsants to Table 4. See Section II.8.2.2 and Section 14.4.4.2.
- Removed PK parameters for [redacted] from Table 6 and Table 7.
- Added information in subsection regarding PK in pediatric patients.

12.4 Microbiology

- Several pUL97 valganciclovir/ganciclovir resistance-associated substitutions confer reduced susceptibility to maribavir and some maribavir resistance-associated substitutions in pUL97 reduce susceptibility to valganciclovir/ganciclovir. Data with respect to resistance and cross-resistance have been updated to adequately address these concerns. See Section II.7.7, Section 18.6, and Section 18.7.
- Antagonism of the antiviral activity was seen with maribavir in combination with valganciclovir/ganciclovir. The label was updated to address this concern. See Section 18.5.

14 CLINICAL STUDIES

14.1 Treatment of Adults with Post-transplant CMV Infection/Disease That Is Refractory (with or without Genotypic Resistance) to Ganciclovir, Valganciclovir, Cidofovir, or Foscarnet

- [redacted] was removed from Table 9 which describes the primary efficacy endpoint analysis at Week 8. See Section [redacted]

- Table 10: Analysis of failures for primary efficacy endpoint comparing LIVTENCITY versus IAT at Week 8 was added. See Section II.6.2.1.4.
- Table 12: Achievement of CMV DNA level <LLOQ and CMV infection symptom control at Week 8, with maintenance through Week 16 was added. Information on other important secondary endpoints (virologic relapse, new onset symptomatic CMV infection, and overall mortality) was added in the text in this section. See Section I.2.1, Section II.6.2.1.3, and Section II.6.2.1.4.
- (b) (4)

22. Postmarketing Requirements and Commitments

The following postmarketing commitment (PMC) and postmarketing requirements (PMRs) were agreed upon by the Applicant:

- PMC 4182-3: A multicenter, randomized, double-blind, double-dummy, active-controlled study to assess the efficacy and safety of maribavir compared to valganciclovir for the treatment of cytomegalovirus infection in Hematologic Stem Cell Transplant Recipients (NCT02927067)

  Study completion: November 2022

  Final report submission: May 2023

- PMR-4182-1: Conduct phenotypic analysis of maribavir against HCMV carrying the following substitutions:

  - High priority: pUL97 M460I/T, A594E/P/T/V, L595F/W, C603R/W/Y
  - Medium priority: pUL97 A440V, V466M, A591V, E596G, K599E, C607F/Y

  Rationale: Known valganciclovir/ganciclovir resistance-associated substitutions for which maribavir susceptibility has not been evaluated. These substitutions have previously been characterized and the constructs/strains should be available (Lurain and Chou 2010; Chou et al. 2020).

  - Low priority:
    - pUL97 P132L, L405P, C518Y , I610T, A613V
    - pUL27 P10L, N289D, H297Y, D298G, N300G, P307L, V310A, D351N, I367V
    - pUL54 S290R, K475R

  (b) (4)

  Rationale: Multiple occurrences in virologic failures.

  Study completion: December 2023

  Final report submission: January 2024

- PMR-4182-2: Determine the gB subtype for each of the subjects in Trial 303.

Study completion: March 2022

Final report submission: April 2022

23. Financial Disclosure

In compliance with the rule of Financial Disclosure by Clinical Investigators, the Applicant provided financial interest information for clinical investigators who participated in the Phase 3 trial (Trial 303) and the supportive Phase 2 trials (Trials 202 and 203), see Table 151, Table 152, and Table 153.

Table 151. Covered Clinical Study, Trial 303

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 933		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Table 152. Covered Clinical Study, Trial: 202

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 182		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Table 153. Covered Clinical Study, Trial 203

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 225		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

24. References

Abbot, 2017, Summary of Safety and Effectiveness Data: PMA P160044, https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160044B.pdf.

Avery, RK, R Arav-Boger, KA Marr, E Kraus, S Shoham, L Lees, B Trollinger, P Shah, R Ambinder, D Neofytos, D Ostrander, M Forman, and A Valsamakis, 2016, Outcomes in Transplant Recipients Treated With Foscarnet for Ganciclovir-Resistant or Refractory Cytomegalovirus Infection, Transplantation, 100(10):e74-80.

Bale, JF, Jr., JR Murph, GJ Demmler, J Dawson, JE Miller, and SJ Petheram, 2000, Intrauterine cytomegalovirus infection and glycoprotein B genotypes, J Infect Dis, 182(3):933-936.

Biron, KK, RJ Harvey, SC Chamberlain, SS Good, AA Smith, 3rd, MG Davis, CL Talarico, WH Miller, R Ferris, RE Dornsife, SC Stanat, JC Drach, LB Townsend, and GW Koszalka, 2002, Potent and selective inhibition of human cytomegalovirus replication by 1263W94, a benzimidazole L-riboside with a unique mode of action, Antimicrob Agents Chemother, 46(8):2365-2372.

Boom, R, CJ Sol, T Schuurman, A Van Breda, JF Weel, M Beld, IJ Ten Berge, PM Wertheim-Van Dillen, and MD De Jong, 2002, Human cytomegalovirus DNA in plasma and serum specimens of renal transplant recipients is highly fragmented, J Clin Microbiol, 40(11):4105-4113.

Chou, S, 2009, Diverse cytomegalovirus UL27 mutations adapt to loss of viral UL97 kinase activity under maribavir, Antimicrob Agents Chemother, 53(1):81-85.

Chou, S, RJ Ercolani, G Marousek, and TL Bowlin, 2013, Cytomegalovirus UL97 kinase catalytic domain mutations that confer multidrug resistance, Antimicrob Agents Chemother, 57(7):3375-3379.

Chou, S, M Hakki, and S Villano, 2012, Effects on maribavir susceptibility of cytomegalovirus UL97 kinase ATP binding region mutations detected after drug exposure in vitro and in vivo, Antiviral Res, 95(2):88-92.

Chou, S and GI Marousek, 2008, Accelerated evolution of maribavir resistance in a cytomegalovirus exonuclease domain II mutant, J Virol, 82(1):246-253.

Chou, S, GI Marousek, AE Senters, MG Davis, and KK Biron, 2004, Mutations in the human cytomegalovirus UL27 gene that confer resistance to maribavir, J Virol, 78(13):7124-7130.

Chou, S, GI Marousek, LC Van Wechel, S Li, and A Weinberg, 2007a, Growth and drug resistance phenotypes resulting from cytomegalovirus DNA polymerase region III mutations observed in clinical specimens, Antimicrob Agents Chemother, 51(11):4160-4162.

Chou, S, K Song, J Wu, T Bo, and C Crumpacker, 2020, Drug resistance mutations and associated phenotypes detected in clinical trials of maribavir for treatment of cytomegalovirus infection, J Infect Dis.

Chou, S, LC Van Wechel, and GI Marousek, 2007b, Cytomegalovirus UL97 Kinase Mutations That Confer Maribavir Resistance, The Journal of Infectious Diseases, 196(1):91-94.

Chou, S, J Wu, K Song, and T Bo, 2019, Novel UL97 drug resistance mutations identified at baseline in a clinical trial of maribavir for resistant or refractory cytomegalovirus infection, Antiviral Res, 172:104616.

Drew, WL, RC Miner, GI Marousek, and S Chou, 2006, Maribavir sensitivity of cytomegalovirus isolates resistant to ganciclovir, cidofovir or foscarnet, J Clin Virol, 37(2):124-127.

Evers, DL, G Komazin, RG Ptak, D Shin, BT Emmer, LB Townsend, and JC Drach, 2004, Inhibition of human cytomegalovirus replication by benzimidazole nucleosides involves three distinct mechanisms, Antimicrob Agents Chemother, 48(10):3918-3927.

Fisher, CE, JL Knudsen, ED Lease, KR Jerome, RM Rakita, M Boeckh, and AP Limaye, 2017, Risk Factors and Outcomes of Ganciclovir-Resistant Cytomegalovirus Infection in Solid Organ Transplant Recipients, Clinical Infectious Diseases, 65(1):57-63.

Hayden, RT, J Preiksaitis, Y Tong, X Pang, Y Sun, L Tang, L Cook, S Pounds, J Fryer, and AM Caliendo, 2015, Commutability of the First World Health Organization International Standard for Human Cytomegalovirus, J Clin Microbiol, 53(10):3325-3333.

Komazin-Meredith, G, S Chou, MN Prichard, CB Hartline, SC Cardinale, K Comeau, JD Williams, AR Khan, NP Peet, and TL Bowlin, 2014, Human cytomegalovirus UL97 kinase is involved in the mechanism of action of methylenecyclopropane analogs with 6-ether and -thioether substitutions, Antimicrob Agents Chemother, 58(1):274-278.

Komazin, G, RG Ptak, BT Emmer, LB Townsend, and JC Drach, 2003a, Resistance of human cytomegalovirus to D- and L-ribosyl benzimidazoles as a tool to identify potential targets for antiviral drugs, Nucleosides Nucleotides Nucleic Acids, 22(5-8):1725-1727.

Komazin, G, RG Ptak, BT Emmer, LB Townsend, and JC Drach, 2003b, Resistance of human cytomegalovirus to the benzimidazole L-ribonucleoside maribavir maps to UL27, J Virol, 77(21):11499-11506.

Kotton, CN, D Kumar, AM Caliendo, S Huprikar, S Chou, L Danziger-Isakov, A Humar, and CMVCG The Transplantation Society International, 2018, The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation, Transplantation, 102(6):900-931.

Lurain, NS and S Chou, 2010, Antiviral drug resistance of human cytomegalovirus, Clin Microbiol Rev, 23(4):689-712.

McGregor, A and KY Choi, 2011, Cytomegalovirus antivirals and development of improved animal models, Expert Opin Drug Metab Toxicol, 7(10):1245-1265.

Preiksaitis, JK, RT Hayden, Y Tong, XL Pang, JF Fryer, AB Heath, L Cook, AK Petrich, B Yu, and AM Caliendo, 2016, Are We There Yet? Impact of the First International Standard for Cytomegalovirus DNA on the Harmonization of Results Reported on Plasma Samples, Clin Infect Dis, 63(5):583-589.

Prichard, MN, WJ Britt, SL Daily, CB Hartline, and ER Kern, 2005, Human cytomegalovirus UL97 Kinase is required for the normal intranuclear distribution of pp65 and virion morphogenesis, J Virol, 79(24):15494-15502.

Qiagen, 2014, Summary of Safety and Effectiveness Data: PMA P130027, https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130027B.pdf.

Razonable, R and A Humar, 2019, Cytomegalovirus in Solid Organ Transplant Recipients – Guidelines of the American Society of Transplantation Infectious Disease Community of Practice, Clinical Transplantation, 33.

Roche, 2017, Summary of Safety and Effectiveness Data: PMA P160041, https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160041B.pdf.

Rodriguez, J, K Casper, G Smallwood, A Stieber, C Fasola, J Lehneman, and T Heffron, 2007, Resistance to combined ganciclovir and foscarnet therapy in a liver transplant recipient with possible dual-strain cytomegalovirus coinfection, Liver Transpl, 13(10):1396-1400.

Tong, Y, XL Pang, C Mabilangan, and JK Preiksaitis, 2017, Determination of the Biological Form of Human Cytomegalovirus DNA in the Plasma of Solid-Organ Transplant Recipients, J Infect Dis, 215(7):1094-1101.

Yong, MK, TL Shigle, Y-J Kim, PA Carpenter, RF Chemaly, and GA Papanicolaou, 2021, American Society for Transplantation and Cellular Therapy Series: #4 - Cytomegalovirus treatment and management of resistant or refractory infections after hematopoietic cell transplantation, Transplantation and Cellular Therapy.

Zipeto, D, C Hong, G Gerna, M Zavattoni, D Katzenstein, TC Merigan, and L Rasmussen, 1998, Geographic and demographic differences in the frequency of human cytomegalovirus gB genotypes 1-4 in immunocompromised patients, AIDS Res Hum Retroviruses, 14(6):533-536.

25. Review Team

Table 154. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Christine Kim, PharmD, RAC-US Alicia Moruf, PharmD, MPH, RAC-US
Nonclinical Reviewer	Ilona Bebenek, PhD, DABT
Nonclinical Team Leader	Laine Peyton Myers, PhD, DABT
Clinical Virology Reviewer	Takashi E. Komatsu, PhD, RAC
Clinical Virology Team Leader	Julian O'Rear, PhD
Office of Clinical Pharmacology Reviewer(s)	Mario Sampson, PharmD Jianghong Fan, PhD Jihye Ahn, PhD
Office of Clinical Pharmacology Team Leader(s)	Vikram Arya, PhD, FCP Manuela Grimstein, PhD Justin Earp, PhD
Clinical Reviewer	Andreas Pikis, MD
Clinical Team Leader	Mary Singer, MD, PhD
Statistical Reviewer	Fraser Smith, PhD
Statistical Team Leader	Thamban Valappil, PhD
Cross-Disciplinary Team Leader	Mary Singer, MD, PhD
Division Director (pharm/tox)	Hanan Ghantous, PhD, DABT
Division Director (OCP)	Kellie Reynolds, PharmD
Division Director (OB)	Dionne Price, PharmD
Division Director (DAV)	Debra Birnkrant, MD
Office Director (OID)	John Farley, MD, MPH

Abbreviations: OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology

Table 155. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Karina Zuck PhD Paresma Patel, PhD Molly Lee, PhD Thomas Oliver, PhD Nathan Davis, PhD Bo Jiang, PhD Qi Zhang, PhD Elsbeth Chikhale, PhD Shamika Brooks, PharmD, Anamitro Banerjee, PhD
OPDP	Nima Ossareh, PharmD, RAC Sam Skariah, PharmD, RAC
OSI	Jenn Sellers, MD, PhD Philip Kronstein, MD
OSE/DEPI	
OSE/DMEPA	Melina Fanari, PharmD Sevan Kolejian, PharmD
OSE/DRM	Naomi Boston, PharmD Cynthia LaCivita, PharmD
DMPP	Jessica Chung, PharmD Barbara Fuller, RN, MSN, CWOCN LaShawn Griffiths, MSHS-PH, BSN, RN
Clinical Data Scientist	Yongqi Li, PhD (former FDA contractor) DeAngelo McKinley, PharmD, PhD (TL)
Medical Editors	Graeme O'May, Megan Young

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DMPP, Division of Medical Policy Programs; DRISK, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations; TL, team lead

Table 156. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical	Andreas Pikis, MD	OND/OID/DAV	2.1,3.2,4,7.2,7.4,7.5,7.6,8.3,10,11,17,20,22,23 X Authored ☐ Approved
Reviewer	**Signature:** Andreas Pikis -S Digitally signed by Andreas Pikis -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Andreas Pikis -S, 0.9.2342.19200300.100.1.1=1300188010 Date: 2021.11.23 09:56:24 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Cross-Disciplinary	Mary Singer, MD, PhD	OND/OID/DAV	Enter sections. X Authored (2.2, 6.3) X Approved
Team Leader	**Signature:** Mary E. Singer -S Digitally signed by Mary E. Singer -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mary E. Singer -S, 0.9.2342.19200300.100.1.1=1300225942 Date: 2021.11.23 09 51:41 -05'00'		
Clinical Virology	Takashi Komatsu, PhD, RAC	OND/OID/DAV	Enter sections. X Authored (5,6,7,18,19) ☐ Approved
Reviewer	**Signature:** Takashi Komatsu -S Digitally signed by Takashi Komatsu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000576976, cn=Takashi Komatsu -S Date: 2021.11.23 10:20:13 -05'00'		
Clinical Virology	Jules O'Rear, PhD	OND/OID/DAV	Enter sections. X Authored (5,6,7,18,19) X Approved(5,6,7,18,19)
Team Leader	**Signature:** Julian J. O'rear -S Digitally signed by Julian J. O'rear -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300150659, cn=Julian J. O'rear -S Date: 2021.11.23 10:31:16 -05'00'		
Clinical Pharmacology	Mario Sampson, PharmD	OTS/OCP/DIDP	Enter sections. X Authored (5, 6, 8, 14) ☐ Approved
Reviewer	**Signature:** Mario Sampson -S Digitally signed by Mario Sampson S DN: c=US o=U S Government ou=HHS ou=FDA ou=People cn=Mario Sampson S 0 9 2342 19200300 100 1 1=2001365806 Date: 2021 11 23 12:14:38 06'00'		
Clinical Pharmacology	Jianghong Fan, PhD	OTS/OCP/DIDP	Enter sections. X Authored (14.4.4) ☐ Approved
Reviewer	**Signature:** Jianghong Fan -S Digitally signed by Jianghong Fan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jianghong Fan -S, 0.9.2342.19200300.100.1.1=2001454698 Date: 2021.11.23 11:59:02 -05'00'		
OCP/ Pharmacometrics	Jihye Ahn, PharmD	OTS/OCP/DPM	Enter sections. X Authored (14.4) ☐ Approved
Reviewer	**Signature:** Jihye Ahn -S (Affiliate) Digitally signed by Jihye Ahn -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001814798, cn=Jihye Ahn -S (Affiliate) Date: 2021.11.23 12:25:27 -05'00'		
Clinical Pharmacology	Vikram Arya, PhD, FCP	OTS/OCP/DIDP	Enter sections. ☐ Authored X Approved (5,6,8,14)
Team Leader	**Signature:** Vikram Arya -S Digitally signed by Vikram Arya -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Vikram Arya -S, 0.9.2342.19200300.100.1.1=1300221914 Date: 2021.11.23 12:46:40 -05'00'		
Clinical Pharmacology	Manuela Grimstein, PhD	OTS/OCP/DIDP	Enter sections. ☐ Authored X Approved (14.4.4)
Team Leader	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
OCP/ Pharmacometrics	Justin Earp, PhD	OTS/OCP/DPM	Enter sections. ☐ Authored X Approved (14.4)
Team Leader	**Signature:** Justin C. Earp -S Digitally signed by Justin C. Earp -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Justin C. Earp -S, 0.9.2342.19200300.100.1.1=1300436664 Date: 2021.11.23 11:22:34 -05'00'		
Clinical Pharmacology	Kellie Reynolds, PharmD	OTS/OCP/DIDP	☐ Authored X Approved(5, 6, 8, 14)
Division Director	**Signature:** Kellie S. Reynolds -S Digitally signed by Kellie S. Reynolds -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300093770, cn=Kellie S. Reynolds -S Date: 2021.11.23 10:47:13 -05'00'		
Statistical	Fraser Smith, PhD	OTS/OB/DBIV	Enter sections. X Authored (6, 15, 16) X Approved
Reviewer	**Signature:** Fraser B. Smith -S Digitally signed by Fraser B. Smith -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300174109, cn=Fraser B. Smith -S Date: 2021.11.23 11:27:49 -05'00'		
Statistical	Dionne Price, PhD	OTS/OB/DBIV	Enter sections. ☐ Authored X Approved
Division Director	**Signature:** Dionne L. Price -S Digitally signed by Dionne L. Price -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300164533, cn=Dionne L. Price -S Date: 2021.11.23 10:40:32 -05'00'		
Cross-Disciplinary	Stacey Min, PharmD	OND/OID/DAV	Enter sections. X Authored (21) ☐ Approved
Associate Director for Labeling	**Signature:** Stacey Min -S Digitally signed by Stacey Min -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Stacey Min -S, 0.9.2342.19200300.100.1.1=2000365089 Date: 2021.11.23 11:14:50 -05'00'		
Cross-Disciplinary	Debra Birnkrant, MD	OND/OID/DAV	Enter sections. ☐ Authored ☐ Approved
Division Director	**Signature:** Debra B. Birnkrant -S Digitally signed by Debra B Birnkrant S DN: c US o U S Government ou HHS ou FDA ou People 0 9 2342 19200300 100 1 1 1300049410 cn Debra B Birnkrant S Date: 2021 11 23 10 07:20 05 00		
Cross-Disciplinary	John Farley, MD, MPH	OND/OID	Enter sections. ☐ Authored ☐ Approved
Signatory Authority	**Signature:**		

Abbreviations: ES, Executive Summary; IA, Interdisciplinary Assessment

Table 157. Signatures of Pharmacology Toxicology Reviewers and Supervisors and Tertiary Personnel

Discipline and Title or Role	***Reviewer Name***	***Office/Divis Banion***	***Sections Authored/ Acknowledged/ Approved***
Reviewer	Ilona Bebenek, PhD, DABT	OID/DPTID	Enter sections. X Authored (7.1, 8.4, 13) □Approved
	Signature: Ilona Bebenek -S Digitally signed by Ilona Bebenek -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ilona Bebenek -S, 0.9.2342.19200300.100.1.1=2001245411 Date: 2021.11.23 11:39:28 -05'00'		
Team Leader	Laine Peyton Myers, PhD, DABT	OID/DPTID	Enter sections. ☐ Authored X Approved (7.1, 8.4, 13)
	Signature: Laine P. Myers -S Digitally signed by Laine P. Myers -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Laine P. Myers -S, 0.9.2342.19200300.100.1.1=1300389063 Date: 2021.11.23 10:12:42 -05'00'		
Director	Hanan Ghantous, PhD, DABT	OID/DPTID	☐ Authored X Approved (7.1, 8.4, 13)
	Signature: Hanan N. Ghantous -S Digitally signed by Hanan N. Ghantous -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300169484, cn=Hanan N. Ghantous -S Date: 2021.11.23 11:56:14 -05'00'		
	Signature:		

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ALICIA MORUF
11/23/2021 01:31:20 PM

JOHN J FARLEY
11/23/2021 03:27:34 PM

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDY

IND/NDA Number:	NDA 215596
Drug Name:	Maribavir (VP 41263)
Indication(s):	Treatment of adults with post-transplant cytomegalovirus (CMV) infection and/or disease, including infections resistant and/or refractory to ganciclovir, valganciclovir, cidofovir or foscarnet.
Studies	Two Year Oral Gavage Carcinogenicity Study in Rats and Mice
Applicant:	Sponsor: Takeda Pharmaceuticals USA Inc 95 Hayden Ave Lexington, Massachusetts 02421, USA. Test facility: (b) (4)
Documents Reviewed:	Electronic submission, dated: March 23, 2021 via SN0001 Electronic data submitted on May 28, 2021 via SN0012
Review Priority:	priority
Biometrics Division:	Division of Biometrics -VI
Statistical Reviewer:	Malick Mbodj, Ph.D.
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Pharmacology-Toxicology for Infectious Diseases
Reviewing Pharmacologist:	Ilona G Bebenek, PhD, DABT
Project Manager:	KIM, CHRISTINE
Keywords:	Carcinogenicity, Dose response

Table of Contents

1. Background

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to assess the carcinogenic potential of VP 41263, when administered orally by gavage at appropriate drug levels for about 104 weeks, in rats and mice. Results of this review have been discussed with the reviewing pharmacologist Dr. Bebenek.

In this review, the phrase "dose response relationship" (trend) refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

2. Rat Study

In this study two separate experiments were conducted, one in male rats and one in female rats. In each of these two experiments there were three treated groups, and two control groups. Three hundred Han Wistar [Crl:WI(Han)] Rats of each sex were assigned to three treated groups, and two control groups by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 60 animals, as indicated in Table 1. The dose levels for treated groups were 10, 30, and 100 mg/kg/day for both males and females. In this review, these dose groups were referred to as the low, medium, and high dose group, respectively. The control groups were exposed to control article only [citrate buffer (0.04M) pH adjusted to 2.6 + 0.3]. administered orally by gavage for about 104 weeks in the same manner as the treated groups.

Table 1: Experimental Design in Rat Study

Group Name	Group N0.	Dose Level (mg/kg/day)		Number of Animal	
		Male	Female	Males	Females
Control 1	1	0	0	60	60
Control 2	2	0	0	60	60
Low	3	10	10	60	60
Medium	4	30	30	60	60
High	5	100	100	60	60

Early final scheduled necropsies were conducted to 97 weeks for males and 92 weeks for females

During the study period all animals were observed for general health/mortality and moribundity twice daily (a.m. and p.m.), abnormal findings were recorded throughout the study. Cage side observations were conducted for each carcinogenicity animal once daily during the dosing phase, except on days when detailed observations were conducted. Detailed observations were conducted for each carcinogenicity animal at least once prior to dosing on Day 1, and weekly thereafter throughout the dosing phase. Detailed examinations for palpable masses were done weekly, the time of onset, location, size, appearance, and progression of each grossly visible or palpable mass, observed in carcinogenicity rats, was recorded weekly, particular attention being paid to the animals during and for the four hours after dosing. Any animal showing signs of severe debility or intoxication, and if determined to be moribund or suffering excessively will be euthanized. Observations will include, but will not be limited to, evaluation for reaction to treatment. Histopathological examinations were performed on all animals found dead or killed moribund or sacrificed at the end of the experiment. Body weights were recorded once during the predose phase, before dosing on Day 1 of the dosing phase, weekly thereafter during the dosing phase, and for each carcinogenic animal of that sex/group during the week of sacrifice.

2.1. Sponsor's analyses

2.1.1. Survival analysis

In the sponsor's analysis, evaluations of trend and heterogeneity of survival data were performed using the Cox-Tarone binary regression on life tables and Gehan-Breslow nonparametric methods using the National Cancer Institute (NCI) Life Table Package (Thomas et al., 1977). The Cox-Tarone method is more sensitive to late deaths, and the Gehan-Breslow method is more sensitive to early deaths due to treatment. Weeks 106 and 105 of the dosing phase were treated as the end of the study in the NCI package for males and females, respectively. Kaplan-Meier product limit survival curves were prepared, and continuity-corrected one-sided tail probabilities for trend and group comparisons were evaluated at <5.0% significance level.

All comparisons were made versus the combined control groups. Tests were performed for dose response (combined controls and dosed groups only), and for each dosed group against combined control groups. The time to death or sacrifice (in weeks) was the dependent variable. Treatment group was included as the strata

Any animal with accidental injury that causes its death, or its unscheduled sacrifice was censored in the estimation. In addition, all animals still alive at the end of the experimental period were censored at the following day.

Sponsor's findings:

Sponsor's analysis showed the numbers of rats surviving to their terminal necropsy were 39 (65%), 44 (73.3%), 38 (63.3%), 41 (68.3%), and 34 (56.7%), in the control 1, control 2, low, medium, and high dose groups, in male rats, respectively, and 32 (53.3%), 32 (53.3%), 34 (56.7%), 36 (60%), and 35 (58.3%), in control 1, control 2, low, medium, and high dose groups, in female rats, respectively. The sponsor's report concluded that there was no statistically significant difference in mortality across the combined control groups and the treated groups in either sex of rats. The pairwise comparisons showed no statistically significant increase or decrease in mortality between the treated groups, and the combined control groups in either sex of rats.

2.1.2. Tumor data analysis

All comparisons were made versus the combined control groups. Tests were performed for dose response (combined controls and dosed groups only), and for each dosed group against combined control groups.

In the sponsor's analysis, tests to compare tumor incidence were performed, with a one-sided risk for increasing incidence with dose. Tests were performed for dose response (combined controls and dosed groups only) and for each dosed group against the combined control groups. Incidental tumors were analyzed by linear logistic regression of tumor prevalence tests (Dinse and Lagakos, 1983). Rapidly lethal and palpable tumors were analyzed in the same manner as survival, using the first palpation time (if applicable) as the tumor onset time.

In the cases where the study pathologist assigned particular occult neoplastic lesions as the cause of death in the animals, IARC type (Peto et al., 1980) of analysis was used by incorporating such information. In the cases of sparse tables, exact form of survival adjusted method of tumor analysis was used.

Site or tumor combinations were statistically analyzed if the incidence in at least one dosed group was increased or decreased by at least two occurrences over the combined control groups. Animals were assigned to the terminal sacrifice strata based on the death or sacrifice status recorded in the data and were not assigned based on the day/week of necropsy.

Adjustment for the multiplicity:

The incidence of tumors was evaluated by the linear trend test (one tailed) at the $p < 0.005$ level for common tumors (an incidence of >1%) and at the $p < 0.025$ level for rare tumors (an incidence of < 1%). Pair-wise comparisons (one-tailed) were evaluated at the $p < 0.01$ level for common tumors and at the $p < 0.05$ level for rare tumors. The incidence rate for defining whether a tumor type is rare or common is based on site-specific background historical data. The Study Pathologist determined whether a tumor type was rare or common.

Sponsor's findings:

Following the multiple testing adjustment method described above, the sponsor's analysis concluded that there were no tumor types with a statistically significant dose response relationship in tumor incidences with increased VP 41263 dose. The pairwise comparisons showed statistically significant increases in the medium and high dose group for the incidences of benign interstitial cell tumor in the testis, when compared to the combined control groups in males ($p = 0.0345$ and 0.0097, respectively). Also, the pairwise comparisons showed a statistically significant increase in the low dose group for the incidences of malignant fibrosarcoma in the skin/subcutaneous, when compared to the combined control groups in males ($p = 0.0292$). For females, the pairwise comparisons showed a statistically significant increase in the low dose group for the incidences of leiomyoma combined with leiomyosarcoma in multiple organs, benign follicular cell adenoma in the thyroid, and follicular cell adenoma combined with carcinoma in the thyroid ($p = 0.0441$, =0.0029, and =0.0011, respectively).

2.2 Reviewer's analyses

To verify sponsor's analysis and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed the survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically on May 28, 2021 via SN0012.

2.2.1 Survival analysis

In the reviewer's analysis, intercurrent mortality data were analyzed using the Kaplan-Meier product limit method. The Kaplan-Meier's curves were presented graphically for male and female rats separately. The dose response relationship and homogeneity of survival distributions were tested for the treatment groups using the Likelihood Ratio test and the Log-Rank test. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for male and female rats, respectively.

Reviewer's findings:

This reviewer's analysis showed the numbers of rats surviving to their terminal necropsy were 39 (65%), 44 (73.3%), 38 (63.3%), 41 (68.3%), and 34 (56.7%), in the control 1, control 2, low, medium, and high

dose groups, in male rats, respectively, and 32 (53.3%), 32 (53.3%), 34 (56.7%), 36 (60%), and 35 (58.3%), in control 1, control 2, low, medium, and high dose groups, in female rats, respectively. This reviewer's analysis showed no statistically significant increase or decrease in mortality across the combined control groups and the three treated groups in either sex of rats. The pairwise comparisons showed no statistically significant increase or decrease in mortality between the treated groups, and the combined control groups in either sex of rats.

2.2.2. Tumor data analysis

In the reviewer's analysis, the tumor data were analyzed for dose response relationship across combined control groups and the treated groups, as well as the pairwise comparisons of combined control groups with each of the treated groups using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method, an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice with development of the tumor type being tested gets a score of s_h =1. An animal that dies at Week w_h without development of the given tumor type before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}} \right)^k$ <1. The adjusted group size is defined as Σs_h . As an interpretation, an animal with score s_h =1 can be considered as a whole animal, while an animal with score s_h <1 can be considered as a partial animal. The adjusted group size Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each animal develops the given tumor being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise comparison) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104-week standard rat and mouse studies, a value of k=3 is suggested in the literature [Gebregziabher and Hoel (2009), Moon et al. (2003), Portier, et al. (1986)]. Hence, this reviewer used k=3 for the analysis of the data. Based on the intent to treat (ITT) principle Wmax was considered as 105 for both male and female rats.

For the calculation of p-values, if there were less than 10 tumor bearing animals across all treatment groups for a given tumor type, the exact tests based on the discrete permutation distribution were used, with dose levels (0, 0, 10, 30, and 100 for both male and female rats) as scores, and asymptotic tests were used for tumor types with higher incidences. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male rats and female rats, respectively.

Multiple testing adjustments:

Following the FDA draft guidance for the carcinogenicity study design and data analysis (2001), for the two-year rat study this reviewer used significance levels of 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

A tumor is defined as a rare tumor if the published spontaneous rate or the spontaneous rate of the combined controls of the tumor is less than 1%, and a common tumor is defined as one with tumor rate greater than or equal to 1%.

Reviewer's findings:

Table 2: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or the pairwise Comparisons **Treated Groups and Control Group in Rats**

Sex	Organ Name	Tumor Name	0 mg Control 1 (N=60)	0 mg Control 2 (N=60)	0 mg (N=120) Control 1+2 P - Trend	10 mg Low (N=60) P - CC vs. L	30 mg Med (N=60) P - CC vs. M	100 mg High (N=60) P - CC vs. H
Male	Skin / Subcutis	M-Fibrosarcoma	0/60 (48) NC	0/60 (54) NC	0/120 (102) 0.4148	3/59 (50) 0.0342*	0/60 (50) NC	1/60 (49) 0.3245
	Testis	B-Interstitial Cell Tumor	0/60 (48) NC	0/60 (54) NC	0/120 (102) 0.0274@	3/60 (50) 0.0342*	3/60 (51) 0.0356*	4/60 (49) 0.0102*
Female	Liver	B-Adenoma, Hepatocellular	1/60 (47) NC	0/60 (45) NC	1/120 (92) 0.0256@	1/60 (49) 0.5759	3/60 (51) 0.1297	4/60 (50) 0.0520
	Pancreas	M-Carcinoma, Islet Cell	0/60 (47) NC	0/60 (45) NC	0/120 (92) 0.8081	3/60 (50) 0.0420*	0/60 (51) NC	0/60 (49) NC
	Thyroid	B-Adenoma, Follicular Cell	1/60 (47) NC	1/60 (45) NC	2/120 (92) 0.4233	7/60 (50) 0.0094*	2/60 (52) 0.4572	3/60 (50) 0.2351
		Adenoma/Carcinoma, Follicular Cell	1/60 (47) NC	1/60 (45) NC	2/120 (92) 0.4767	8/60 (50) 0.0037*	3/60 (52) 0.2495	3/60 (50) 0.2351
	Vagina	B-Polyp, stromal	0/60 (47) NC	0/60 (45) NC	0/120 (92) 0.0420@	0/60 (49) NC	0/60 (51) NC	2/60 (50) 0.1224

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable
@: not statistically significant at 0.005 and 0.025 level for common and rare tumor or 0.01 and 0.05 level for common and rare tumors for tests of dose response relationship and pairwise comparison, respectively.
*: Statistically significant at 0.005 and 0.025 level for common and rare tumor or 0.01 and 0.05 level for common and rare tumors for tests of dose response relationship and pairwise comparison, respectively.

Following the multiple testing adjustment method described above, this reviewer's analysis showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased VP 41263 dose. The pairwise comparisons showed statistically significant increases in low dose group for the incidence of malignant fibrosarcoma in the skin/subcutaneous, (p = 0.0342), when compared to the combined controls in male rats. Also, in male rats, the pairwise comparisons showed statistically significant increases in low, medium and high dose group for the incidences of benign interstitial cell tumor in the testis, (p = 0.0342, =0.0356, and =0.0102, respectively), when compared to the combined control groups.

In female rats, the pairwise comparisons showed statistically significant increases in the low dose group for the incidences of malignant carcinoma islet cell in the pancreas, of benign follicular cell adenoma and the combined benign follicular cell adenoma and malignant follicular cell carcinoma in the thyroid, (p = 0.0420, =0.0094, and = 0.0037 respectively), when compared to the combined control groups.

3. Mouse Study

Two separate experiments were conducted, one in male mice and one in female mice. In each of these two experiments three treated groups, and two control groups. Three hundred CD-1 mice of each sex were assigned to three treated groups, and two control groups by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 60 animals, as indicated in Table 3. The dose levels for treated groups were 25, 75, and 150 mg/kg/day for both males and females. In this review, these dose groups were referred to as the low, medium, and high dose group, respectively. The control groups were exposed to control Item only [citrate buffer (0.04M) pH adjusted to 2.6 ± 0.3]. administered orally by gavage for about 104 weeks in the same manner as the treated groups.

During the first 45 weeks of the study a higher than expected mortality rate occurred, which raised concern that there may be insufficient numbers of animals in the high-dose groups, and possibly the mid-dose groups, to successfully reach adequate survival at 104 weeks. Consequently, to ensure sufficient survival for animals in the mid- and high-dose groups, the study design was changed (based on FDA recommendation), starting on Day 372 of the dosing phase the remaining toxicokinetic animals dosed at 75 or 150 mg/kg/day (Groups 8 and 9, respectively) through the 2-year dosing phase i.e, 19 males from Group 8 and 17 males from Group 9 were transferred to Groups 4 and 5, respectively; similarly, for females, 21 animals from Group 8 and 15 animals from Group 9 were transferred to Groups 4 and 5, respectively. However, only 18 males from Group 8 and 14 females from Group 9 were microscopically examined.

Table 3: Experimental Design in Mouse Study

Group Name	Group N0.	Dose Level (mg/kg/day)		Number of Animal	
		Male	Female	Males	Females
Control 1	1	0	0	60	60
Control 2	2	0	0	60	60
Low	3	25	25	60	60
Medium	4	75	75	79^	81^
High	5	150	150	77^	75^

^ Beginning Week 54 (Day 372), surviving toxicokinetic animals in medium dose group, Group 8 (19 males and 21 females) and in high dose group, Group 9 (17 males and 15 females) were treated as carcinogenicity animals. However, only 18 males from Group 8 and 14 females from Group 9 were microscopically examined.

Animals were checked twice daily (a.m. and p.m.) for mortality, abnormalities, and signs of pain or distress., abnormal findings were recorded throughout the study. Detailed observations were conducted for each carcinogenicity animal, including toxicokinetic animals in medium and high dose groups, beginning during Week 54 of the dosing phase, at least once during the pre-dose phase, prior to dosing on Day 1, and weekly thereafter throughout the dosing phase, and on the day of scheduled sacrifice. Observations will include, but will not be limited to, evaluation for reaction to treatment. The time of onset, location, size, appearance, and progression of each grossly visible or palpable mass, observed in carcinogenicity mice, was recorded at the same intervals as detailed observations, particular attention being paid to the animals during and for the first hour after dosing. Any animal showing signs of severe debility or intoxication, and if determined to be moribund or suffering excessively will be euthanized. Histopathological examinations were performed on all animals found dead, killed moribund, or sacrificed at the end of the experiment. Body weights were recorded once during the pre-dose phase, before dosing on Day 1, weekly thereafter (based on Day 1) to Week 14 during the dosing phase, and every 4 weeks thereafter, and during Week 105 of the dosing phase.

3.1. Sponsor's analyses

3.1.1 Survival analysis

The sponsor used similar methodologies to analyze the Mouse survival data as those used to analyze the rat survival data.

Sponsor’s findings:

Sponsor’s analysis showed the numbers of mice surviving to their terminal necropsy (including surviving toxicokinetic animals in medium and high dose group at week 54) were 37 (61.7%), 29 (48.3%), 34 (56.7%), 35 (44.8%), and 34 (44.2%), in the control 1, control 2, low, medium, and high dose groups in

male mice, respectively, and 28 (46.7%), 31 (51.7%), 25 (41.7%), 37 (45.7%), and 22 (29.7%), in female mice, respectively. The sponsor's report concluded that there was a significant positive trend in mortality in male mice by the Cox-Tarone ($0.0238 \leq p \leq 0.0258$) and Gehan-Breslow ($p = 0.0193$) tests, along with a significant increase in the mortality rate for males given 150 mg/kg/day when compared with the combined controls by the Gehan-Breslow test ($p = 0.0403$) .

Also the sponsor's report concluded that there was a significant positive trend in mortality in female mice by the Cox-Tarone ($0.0043 \leq p \leq 0.0047$) and Gehan-Breslow ($p = 0.0011$) tests, along with a significant increase in the mortality rate for females given 150 mg/kg/day when compared with the combined controls by the Cox-Tarone test ($p = 0.0031$) and Gehan-Breslow test ($p = 0.0007$).

3.1.2 Tumor data analysis

The sponsor used similar methodologies to analyze the Mouse tumor data as those used to analyze the rat tumor data.

Multiple testing adjustment:

For multiplicity adjustment testing, the sponsor used similar test levels of significance as those used for rat study to adjust for multiple testing.

Sponsor's findings:

following the multiple testing adjustment method described above, the sponsor analysis showed statistically significant increasing dose response relationships across the combined controls and the treated groups, for the incidence of hemangiosarcoma, hemangioma combined with hemangiosarcoma in the multiple organs, of bronchiolar-alveolar adenocarcinoma found in lung with bronchi, in male mice and the incidence of adenocarcinoma in the uterus in female mice, ($p = 0.0018$, $p = 0.0001$, $p = 0.0021$, and $p = 0.0048$, respectively). The pairwise comparisons showed statistically significant increases in high dose group, for the incidence of hemangiosarcoma, hemangioma combined with hemangiosarcoma in the multiple organs, of bronchiolar-alveolar adenocarcinoma found in lung with bronchi, in male mice and the incidence of adenocarcinoma, adenoma combined with adenocarcinoma in the uterus, in female mice, ($p = 0.0018$, $p=0.0001$, $p = 0.0066$, and $p = 0.0037$, 0.0037, respectively). Also, the pairwise comparisons showed statistically significant increases in medium dose group, for the incidence of bronchiolar-alveolar adenocarcinoma found in lung with bronchi, hepatocellular carcinoma found in the liver, in male mice and the incidence of adenoma combined with adenocarcinoma in the uterus, in female mice, ($p = 0.0232$, $p=0.0180$, and $p = 0.0429$, respectively).

Statistically significant decreases noted in the medium dose group compared with combined controls for hepatocellular adenoma found in the liver in males and hemangiosarcoma found in multiple organs in females.

3.2 Reviewer's analyses

Similar to the rat study, this reviewer independently performed the survival and tumor data analyses of the mouse study. For the analysis of the survival data and the tumor data of the mouse study, this reviewer used similar methodologies that were used for the analyses of the survival and tumor data of the rat study. Data used in this reviewer's analyses were provided by the sponsor electronically. Beginning Week 54 (Day 372), surviving toxicokinetic animals in medium dose group, Group 8 (19 males and 21 females) and in high dose

group, Group 9 (17 males and 15 females) were treated as carcinogenicity animals. However, only 18 males from Group 8, and 14 females from Group 9 were microscopically examined.

3.2.1 Survival analysis

The intercurrent mortality data are given in Tables 4A and 4B in the appendix for male and female mice, respectively. The Kaplan-Meier curves for death rate are given in Figures 2A and 2B in the appendix for male and female mice, respectively. Results for test of dose response relationship and homogeneity of survivals among treatment groups are given in Tables 5A and 5B in the appendix for male and female mice, respectively.

Reviewer's findings:

This reviewer's analysis showed the numbers of mice surviving to their terminal necropsy (including surviving toxicokinetic animals in medium and high dose group at week 54) were 37 (61.7%), 29 (48.3%), 34 (56.7%), 35 (44.8%), and 34 (44.2%), in the control 1, control 2, low, medium, and high dose groups in male mice, respectively, and 28 (46.7%), 31 (51.7%), 25 (41.7%), 37 (45.7%), and 22 (29.7%), in female mice, respectively. This reviewer's analysis showed a statistically significant increase in mortality across the combined control groups and the three treated groups in female mice (p value =0.0103). The pairwise comparisons also showed statistically significant increase in mortality between the high dose group, and the combined control groups in female mice (p value =0.0063).

3.2.2 Tumor data analysis

The tumor rates and the p-values of the tumor types tested for dose response relationship and the pairwise comparisons of combined controls and treated groups are given in Table 6A and 6B in the appendix for male and female mice, respectively.

Multiple testing adjustment:

For multiplicity adjustment testing, this reviewer used similar test levels of significance as those used for rat study to adjust for multiple testing, (FDA 2001 draft guidance for the carcinogenicity study design and data analysis).

Reviewer's findings:

Table 4: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or the pairwise Comparisons **Treated Groups and Control Group in Mouse.**

Sex	Organ Name	Tumor Name	0 mg Control 1 (N=60)	0 mg Control 2 (N=60)	0 mg (N=120) Control 1+2 P - Trend	25 mg Low (N=60) P - CC vs. L	75 mg Med (N=78) P - CC vs. M	150 mg High (N=77) P - CC vs. H
Male	Liver	Hemangiosarcoma	3/60 (45) NC	1/60 (42) NC	4/120 (87) 0.0303@	2/60 (46) 0.6785	1/78 (57) 0.9232	7/77 (51) 0.0587
		Hepatocellular Carcinoma	4/60 (45) NC	3/60 (42) NC	7/120 (87) 0.2595	5/60 (47) 0.4171	11/78 (58) 0.0461@	5/77 (50) 0.4605
	Lung with Bronchi	Bronchiolo-Alveolar Adenocarcinoma	2/60 (46) NC	3/60 (42) NC	5/120 (88) 0.0043*	2/60 (46) 0.7617	9/78 (58) 0.0471@	9/77 (49) 0.0218@
	Whole Body	Hemangioma/ Hemangiosarcoma	4/60 (45) NC	1/60 (42) NC	5/120 (87) 0.0002*	4/60 (46) 0.3784	5/78 (58) 0.3632	14/77 (52) 0.0006*

Sex	Organ Name	Tumor Name	0 mg Control 1 (N=60)	0 mg Control 2 (N=60)	0 mg (N=120) Control 1+2 P - Trend	25 mg Low (N=60) P - CC vs. L	75 mg Med (N=78) P - CC vs. M	150 mg High (N=77) P - CC vs. H
Female	Uterus	Adenocarcinoma	0/60 (44) NC	0/60 (47) NC	0/120 (91) 0.0109*	1/60 (43) 0.3209	1/81 (61) 0.4013	3/74 (40) 0.0270*

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable
*: Statistically significant at 0.005 and 0.025 level for common and rare tumor or 0.01 and 0.05 level for common and rare tumors for tests of dose response relationship and pairwise comparison, respectively.
@: not Statistically significant at 0.005 and 0.025 level for common and rare tumor or 0.01 and 0.05 level for common and rare tumors for tests of dose response relationship and pairwise comparison, respectively

Following the multiple testing adjustment method described above, this reviewer's analyses showed statistically significant increasing dose response relationships across the combined controls and the treated groups for the incidence of bronchiolo-alveolar adenocarcinoma in lung with bronchi, of the combined hemangioma and hemangiosarcoma in whole body, in male mice and the incidence of adenocarcinoma in the uterus, in female mice (p-values = 0.0043, 0.0002, and =0.0109, respectively). The pairwise comparisons showed statistically significant increases in the high dose group for the incidences of the combined hemangioma and hemangiosarcoma in whole body in male mice, and adenocarcinoma in the uterus in female mice (p-values =0.0006, and = 0.0270).

4. Summary

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in mice. These studies were intended to assess the carcinogenic potential of VP 41263 in rats and mice when administered orally by gavage at appropriate drug levels for about 104 weeks.

Rat Study:

In this study two separate experiments were conducted, one in male rats and one in female rats. In each of these two experiments there were three treated groups, and two control groups. Three hundred Han Wistar [Crl:WI(Han)] Rats of each sex were assigned to three treated groups, and two control groups by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 60 animals, as indicated in Table 1. The dose levels for treated groups were 10, 30, and 100 mg/kg/day for both males and females. In this review, these dose groups were referred to as the low, medium, and high dose group, respectively. The control groups were exposed to control article only [citrate buffer (0.04M) pH adjusted to 2.6 + 0.3]. administered orally by gavage for about 104 weeks in the same manner as the treated groups.

This reviewer's analysis showed the numbers of rats surviving to their terminal necropsy were 39 (65%), 44 (73.3%), 38 (63.3%), 41 (68.3%), and 34 (56.7%), in the control 1, control 2, low, medium, and high dose groups, in male rats, respectively, and 32 (53.3%), 32 (53.3%), 34 (56.7%), 36 (60%), and 35 (58.3%), in female rats, respectively. This reviewer's analysis showed no statistically significant increase or decrease in mortality across the combined control groups and the three treated groups in either sex of rats. The pairwise comparisons showed no statistically significant increase or decrease in mortality between the treated groups, and the combined control groups in either sex of rats.

For tumor data, this reviewer's analysis showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased VP 41263dose. The pairwise comparisons showed statistically significant increases in low dose group for the incidence of malignant fibrosarcoma in the

skin/subcutaneous, (p = 0.0342), when compared to the combined controls in male rats. Also, in male rats, the pairwise comparisons showed statistically significant increases in low, medium and high dose group for the incidences of benign interstitial cell tumor in the testis, (p = 0.0342, =0.0356, and =0.0102, respectively), when compared to the combined control groups.

In female rats, the pairwise comparisons showed statistically significant increases in the low dose group for the incidences of malignant carcinoma islet cell in the pancreas, of benign follicular cell adenoma and the combined benign follicular cell adenoma and malignant follicular cell carcinoma in the thyroid, (p = 0.0420, =0.0094, and = 0.0037 respectively), when compared to the combined control groups.

Mouse Study:

Two separate experiments were conducted, one in male mice and one in female mice. In each of these two experiments three treated groups, and two control groups. Three hundred CD-1 mice of each sex were assigned to three treated groups, and two control groups by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 60 animals, as indicated in Table 3. The dose levels for treated groups were 25, 75, and 150 mg/kg/day for both males and females. In this review, these dose groups were referred to as the low, medium, and high dose group, respectively. The control groups were exposed to control Item only [citrate buffer (0.04M) pH adjusted to 2.6 ± 0.3]. administered orally by gavage for about 104 weeks in the same manner as the treated groups.

During the first 45 weeks of the study a higher than expected mortality rate occurred, which raised concern that there may be insufficient numbers of animals in the high-dose groups, and possibly the mid-dose groups, to successfully reach adequate survival at 104 weeks. Consequently, to ensure sufficient survival for animals in the mid- and high-dose groups, the study design was changed (based on FDA recommendation), starting on Day 372 of the dosing phase the remaining toxicokinetic animals dosed at 75 or 150 mg/kg/day (Groups 8 and 9, respectively) i.e, 19 males from Group 8 and 17 males from Group 9 were transferred to Groups 4 and 5, respectively; similarly, for females, 21 animals from Group 8 and 15 animals from Group 9 were transferred to Groups 4 and 5, respectively. However, only 18 males from Group 8 and 14 females from Group 9 were microscopically examined.

This reviewer's analysis showed the numbers of mice surviving to their terminal necropsy (including surviving toxicokinetic animals in medium and high dose group at week 54) were 37 (61.7%), 29 (48.3%), 34 (56.7%), 35 (44.9%), and 34 (44.2%), in the control 1, control 2, low, medium, and high dose groups in male mice, respectively, and 28 (46.7%), 31 (51.7%), 25 (41.7%), 37 (45.7%), and 22 (29.7%), in female mice, respectively. This reviewer's analysis showed a statistically significant increase in mortality across the combined control groups and the three treated groups in female mice (p value =0.0103). The pairwise comparisons also showed statistically significant increase in mortality between the high dose group, and the combined control groups in female mice (p value =0.0063).

For tumor data, following the multiple testing adjustment method described above, this reviewer's analyses showed statistically significant increasing dose response relationships across the combined controls and the treated groups for the incidence of bronchiolo-alveolar adenocarcinoma in lung with bronchi, of the combined hemangioma and hemangiosarcoma in whole body, in male mice and the incidence of adenocarcinoma in the uterus, in female mice (p-values = 0.0043, 0.0002, and =0.0109, respectively). The pairwise comparisons showed statistically significant increases in the high dose group for the incidences of the combined hemangioma and hemangiosarcoma in whole body in male mice, and adenocarcinoma in the uterus in female mice (p-values =0.0006, and = 0.0270),

Malick Mbodj, Ph.D.
Mathematical Statistician

Concur: Karl Lin, Ph.D. Team Leader, DBVI

cc:
Archival NDA 215596- VP 41263
Dr. Tsong Dr. Bebenek
Dr. Lin KIM, CHRISTINE
Dr. Rahman Dr. (b) (4)

5. Appendix

Table1A: Intercurrent Mortality Rate
Male Rats

	0mg|kg|day Control 1		0mg|kg|day Control 2		10 mg|kg|day Low		30 mg|kg|day Med		100 mg|kg|day High	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	5	8.33	.	.	6	10.00	2	3.33	1	1.67
53 - 78	5	16.67	3	5.00	4	16.67	4	10.00	6	11.67
79 - 92	4	23.33	4	11.67	3	21.67	6	20.00	6	21.67
93 - 105	6	33.33	6	21.67	9	36.67	5	28.33	10	38.33
ADD	1	1.67	3	5.00	.	.	2	3.34	3	5.00
Ter. Sac.	39	65.00	44	73.33	38	63.33	41	68.33	34	56.67
Total	60	100.00	60	100.00	60	100.00	60	100.00	60	100.00

Animals were assigned to the terminal sacrifice strata based on the death or sacrifice status recorded
ADD: accidental death

Table1B: Intercurrent Mortality Rate
Female Rats

	0mg|kg|day Control 1		0mg|kg|day Control 2		10 mg|kg|day Low		30 mg|kg|day Med		100 mg|kg|day High	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	4	6.67	3	5.00	2	3.33	1	1.67	.	.
53 - 78	4	13.33	7	16.67	7	15.00	2	5.00	7	11.67
79 - 92	10	30.00	13	38.33	5	23.33	11	23.33	7	23.33
93 - 104	10	46.67	3	43.33	12	43.33	10	40.00	9	38.33
ADD	.	.	2	3.34	.	.	.	.	2	3.34
Ter. Sac.	32	53.33	32	53.33	34	56.67	36	60.00	35	58.33
Total	60	100.00	60	100.00	60	100.00	60	100.00	60	100.00

Animals were assigned to the terminal sacrifice strata based on the death or sacrifice status recorded
ADD: accidental death

Table 2A: Intercurrent Mortality Comparison for
Male Rats

Test Statistics	**P-value for Combined Cont. Low, Med, high**	**P-value for Combined Cont. vs Low**	**P-value for Combined Cont. vs Med**	**P-value for Combined Cont. vs High**
Dose-Response (Likelihood Ratio)	0.2330	0.2329	0.8684	0.1487
Homogeneity (Log-Rank)	0.3871	0.2229	0.8674	0.1388

Table 2B: Intercurrent Mortality Comparison for
Female Rats

Test Statistics	**P-value for Combined Cont. Low, Med, high**	**P-value for Combined Cont. vs Low**	**P-value for Combined Cont. vs Med**	**P-value for Combined Cont. vs High**
Dose-Response (Likelihood Ratio)	0.3401	0.5945	0.3188	0.3184
Homogeneity (Log-Rank)	0.6629	0.5939	0.3212	0.3206

Table3A: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons

Male Rats Poly-3

Organ Name	Tumor Name	0 mg Control 1 (N=60)	0 mg Control 2 (N=60)	0 mg (N=120) Control 1+2 P - Trend	10 mg Low (N=60) P -CC vs. L	30 mg Med (N=60) P -CC vs. M	100 mg High (N=60) P -CC vs. H
Adipose Tissue	B-Hibernoma, Benign	2/60 (50) NC	1/60 (55) NC	3/120 (105) 0.4960	0/60 (49) 1.0000	2/60 (51) 0.5284	1/60 (50) 0.7933
	B-Lipoma	1/60 (48) NC	0/60 (54) NC	1/120 (102) 1.0000	0/60 (49) 1.0000	0/60 (50) 1.0000	0/60 (49) 1.0000
	M-Hibernoma, Malignant	1/60 (48) NC	1/60 (54) NC	2/120 (102) 0.4880	0/60 (49) 1.0000	0/60 (50) 1.0000	1/60 (50) 0.7008
Adrenal, Medulla	B-Pheochromocytoma	1/60 (48) NC	0/60 (54) NC	1/120 (102) 0.1353	1/60 (49) 0.5452	0/60 (50) 1.0000	2/60 (49) 0.2460
	M-Malignant Ganglioneuroma	0/60 (48) NC	0/60 (54) NC	0/120 (102) 0.3984	0/60 (49) NC	1/60 (51) 0.3333	0/60 (49) NC
	M-Malignant Pheochromocytoma	1/60 (48) NC	0/60 (54) NC	1/120 (102) 0.6826	1/60 (50) 0.5512	1/60 (51) 0.5570	0/60 (49) 1.0000
Body, Whole / Cavity	B-Angioma	1/60 (48) NC	0/60 (54) NC	1/120 (102) 1.0000	0/60 (49) 1.0000	0/60 (50) 1.0000	0/60 (49) 1.0000
	B-Hemangioma	2/60 (49) NC	4/60 (54) NC	6/120 (103) 0.1950	4/60 (49) 0.4098	3/60 (52) 0.6337	5/60 (49) 0.2555
	M-Hemangiosarcoma	0/60 (48) NC	1/60 (54) NC	1/120 (102) 1.0000	0/60 (49) 1.0000	0/60 (50) 1.0000	0/60 (49) 1.0000
	M-Histiocytic Sarcoma	0/60 (48) NC	0/60 (54) NC	0/120 (102) 0.5839	2/60 (50) 0.1067	1/60 (51) 0.3333	0/60 (49) NC
	M-Lymphosarcoma	2/60 (50) NC	1/60 (54) NC	3/120 (104) 0.3875	2/60 (51) 0.5326	0/60 (50) 1.0000	2/60 (49) 0.5149
	M-Malignant Mesothelioma	0/60 (48) NC	0/60 (54) NC	0/120 (102) 0.1171	0/60 (49) NC	1/60 (51) 0.3333	1/60 (49) 0.3245
Brain	B-Granular Cell Tumor	0/60 (48) NC	0/60 (54) NC	0/120 (102) 0.5839	2/60 (50) 0.1067	1/60 (51) 0.3333	0/60 (49) NC
	M-Malignant Astrocytoma	0/60 (48) NC	0/60 (54) NC	0/120 (102) 0.1165	0/60 (49) NC	1/60 (50) 0.3289	1/60 (49) 0.3245
	M-Malignant Granular Cell Tumor	0/60 (48) NC	1/60 (54) NC	1/120 (102) 1.0000	0/60 (49) 1.0000	0/60 (50) 1.0000	0/60 (49) 1.0000
Cavity, Abdominal	M-Liposarcoma	0/60 (48) NC	0/60 (54) NC	0/120 (102) 0.5936	1/60 (50) 0.3289	0/60 (50) NC	0/60 (49) NC
Gl, Harderian	M-Carcinoma, Squamous Cell	0/60 (48) NC	0/60 (54) NC	0/120 (102) 0.3984	0/60 (49) NC	1/60 (51) 0.3333	0/60 (49) NC
Gl, Zymbal's	M-Carcinoma	0/60 (48) NC	0/60 (54) NC	0/120 (102) 0.1905	1/60 (50) 0.3289	0/60 (50) NC	1/59 (48) 0.3200

Male Rats Poly-3

Organ Name	Tumor Name	0 mg Control 1 (N=60)	0 mg Control 2 (N=60)	0 mg (N=120) Control 1+2 P - Trend	10 mg Low (N=60) P -CC vs. L	30 mg Med (N=60) P -CC vs. M	100 mg High (N=60) P -CC vs. H
Heart	M-Endocardial Schwannoma	0/60 (48) NC	1/60 (54) NC	1/120 (102) 0.8352	2/60 (49) 0.2460	0/60 (50) 1.0000	0/60 (49) 1.0000
Jejunum	M-Carcinoma	0/60 (48) NC	1/60 (54) NC	1/120 (102) 0.6361	0/60 (49) 1.0000	1/58 (50) 0.5512	0/60 (49) 1.0000
	M-Fibrosarcoma	0/60 (48) NC	1/60 (54) NC	1/120 (102) 1.0000	0/60 (49) 1.0000	0/58 (50) 1.0000	0/60 (49) 1.0000
Kidney	M-Carcinoma, Tubule Cell	0/60 (48) NC	0/60 (54) NC	0/120 (102) 0.1960	0/60 (49) NC	0/60 (50) NC	1/60 (49) 0.3245
Liver	B-Adenoma, Hepatocellular	1/60 (49) NC	0/60 (54) NC	1/120 (102) 0.1311	1/60 (49) 0.5452	2/60 (51) 0.2578	2/60 (49) 0.2460
	B-Cholangioma	1/60 (48) NC	0/60 (54) NC	1/120 (102) 1.0000	0/60 (49) 1.0000	0/60 (50) 1.0000	0/60 (49) 1.0000
	M-Carcinoma, Hepatocellular	0/60 (48) NC	0/60 (54) NC	0/120 (102) 0.5920	1/60 (49) 0.3245	0/60 (50) NC	0/60 (49) NC
Lung	B-Adenoma, Bronchiolar-Alveolar	1/60 (48) NC	0/60 (54) NC	1/120 (102) 0.8352	2/60 (49) 0.2460	0/60 (50) 1.0000	0/60 (49) 1.0000
	M-Carcinoma, Bronchiolar-Alveolar	0/60 (48) NC	0/60 (54) NC	0/120 (102) 0.5920	1/60 (49) 0.3245	0/60 (50) NC	0/60 (49) NC
Mammary, Male	M-Carcinoma	0/58 (46) NC	0/60 (54) NC	0/118 (100) 0.5833	1/57 (47) 0.3197	0/57 (47) NC	0/57 (46) NC
Pancreas	B-Adenoma, Islet Cell	3/60 (49) NC	2/60 (54) NC	5/120 (103) 0.5112	1/59 (49) 0.9078	2/60 (51) 0.7387	2/60 (49) 0.7220
	M-Carcinoma, Islet Cell	0/60 (48) NC	1/60 (54) NC	1/120 (102) 1.0000	0/59 (49) 1.0000	0/60 (50) 1.0000	0/60 (49) 1.0000
Parathyroid	B-Adenoma	0/60 (48) NC	0/59 (53) NC	0/119 (101) 0.4573	1/57 (47) 0.3176	1/57 (49) 0.3267	0/55 (45) NC
	M-Carcinoma	0/60 (48) NC	0/59 (53) NC	0/119 (101) 0.1860	0/57 (47) NC	0/57 (49) NC	1/55 (45) 0.3082
Pituitary	B-Adenoma	19/60 (52) NC	18/60 (56) NC	37/120 (108) 0.0907	19/60 (51) 0.4218	13/60 (51) 0.9034	25/60 (55) 0.1113
	B-Adenoma, Pars Nervosa	0/60 (48) NC	1/60 (54) NC	1/120 (102) 1.0000	0/60 (49) 1.0000	0/60 (50) 1.0000	0/60 (49) 1.0000
Skin/Subcutis	B-Adenoma, Sebaceous Gland	0/60 (48) NC	1/60 (54) NC	1/120 (102) 0.8345	1/59 (49) 0.5452	0/60 (50) 1.0000	0/60 (49) 1.0000
	B-Fibroma	0/60 (48) NC	1/60 (54) NC	1/120 (103) 0.6849	1/59 (49) 0.5423	3/60 (51) 0.1063	0/60 (49) 1.0000
	B-Keratoacanthoma	1/60 (48) NC	0/60 (54) NC	1/120 (102) 0.4042	2/59 (49) 0.2460	1/60 (50) 0.5512	1/60 (49) 0.5452

Male Rats Poly-3

Organ Name	Tumor Name	0 mg Control 1 (N=60)	0 mg Control 2 (N=60)	0 mg (N=120) Control 1+2 P - Trend	10 mg Low (N=60) P -CC vs. L	30 mg Med (N=60) P -CC vs. M	100 mg High (N=60) P -CC vs. H
	B-Papilloma, Squamous Cell	0/60 (48) NC	2/60 (54) NC	2/120 (102) 0.7925	0/59 (48) 1.0000	1/60 (51) 0.7066	0/60 (49) 1.0000
	M-Carcinoma, Basal Cell	0/60 (48) NC	0/60 (54) NC	0/120 (102) 0.4738	1/59 (48) 0.3200	1/60 (51) 0.3333	0/60 (49) NC
	M-Carcinoma, Squamous Cell	1/60 (48) NC	0/60 (54) NC	1/120 (102) 1.0000	0/59 (48) 1.0000	0/60 (50) 1.0000	0/60 (49) 1.0000
	M-Fibrosarcoma	0/60 (48) NC	0/60 (54) NC	0/120 (102) 0.4148	3/59 (50) 0.0342*	0/60 (50) NC	1/60 (49) 0.3245
	M-Osteosarcoma	0/60 (48) NC	0/60 (54) NC	0/120 (102) 0.1968	0/59 (48) NC	0/60 (50) NC	1/60 (49) 0.3245
Stomach, Gl	M-Sarcoma	0/60 (48) NC	0/60 (54) NC	0/120 (102) 0.1960	0/60 (49) NC	0/60 (50) NC	1/60 (49) 0.3245
Stomach, Nonglandular	M-Leiomyosarcoma	0/60 (48) NC	0/60 (54) NC	0/120 (102) 0.5936	1/60 (50) 0.3289	0/60 (50) NC	0/60 (49) NC
Testis	B-Interstitial Cell Tumor	0/60 (48) NC	0/60 (54) NC	0/120 (102) 0.0274	3/60 (50) 0.0342*	3/60 (51) 0.0356*	4/60 (49) 0.0102*
Thymus	B-Thymoma	1/56 (45) NC	1/59 (53) NC	2/115 (99) 0.7769	0/57 (46) 1.0000	1/55 (45) 0.6782	0/55 (46) 1.0000
	M-Malignant Thymoma	0/56 (45) NC	1/59 (53) NC	1/115 (98) 0.1332	1/57 (46) 0.5384	0/55 (45) 1.0000	2/55 (46) 0.2393
Thyroid	B-Adenoma, C-Cell	7/60 (49) NC	4/60 (55) NC	11/120 (104) 0.1079	9/60 (50) 0.1522	5/60 (51) 0.6576	10/60 (51) 0.0996
	B-Adenoma, Follicular Cell	3/60 (48) NC	5/60 (54) NC	8/120 (103) 0.3807	2/60 (49) 0.8907	4/60 (51) 0.6070	4/59 (49) 0.5806
	M-Carcinoma, C-Cell	0/60 (48) NC	0/60 (54) NC	0/120 (102) 0.1928	0/60 (49) NC	0/60 (50) NC	1/59 (48) 0.3200
	M-Carcinoma, Follicular Cell	1/60 (48) NC	2/60 (54) NC	3/120 (102) 0.5855	0/60 (49) 1.0000	0/60 (50) 1.0000	1/59 (48) 0.7903
	B-Adenoma/ M-Carcinoma, Follicular	4/60 (48) NC	7/60 (55) NC	11/120 (103) 0.4136	2/60 (49) 0.9609	4/60 (51) 0.7989	5/59 (49) 0.6355

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable
*: Statistically significant at 0.005 and 0.025 level for common and rare tumor or 0.01 and 0.05 level for common and rare tumors for tests of dose response relationship and pairwise comparison, respectively

Table3B: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons

Female Rats **Poly-3 Test**

Organ Name	Tumor Name	0 mg Control 1 (N=60)	0 mg Control 2 (N=60)	0 mg (N=120) Control 1+2 P - Trend	10 mg Low (N=60) P -CC vs. L	30 mg Med (N=60) P -CC vs. M	100 mg High (N=60) P - CC vs. H
Adipose Tissue	M-Hibernoma, Malignant	3/60 (49) NC	0/60 (45) NC	3/120 (94) 0.4223	2/60 (50) 0.5689	2/60 (52) 0.5862	2/60 (51) 0.5776
	M-Liposarcoma	0/60 (47) NC	1/60 (46) NC	1/120 (92) 1.0000	0/60 (49) 1.0000	0/60 (51) 1.0000	0/60 (49) 1.0000
Adrenal, Cortex	B-Lipoma	1/60 (47) NC	0/60 (45) NC	1/120 (92) 1.0000	0/59 (49) 1.0000	0/60 (51) 1.0000	0/60 (49) 1.0000
Adrenal, Medulla	B-Pheochromocytoma	0/60 (47) NC	0/60 (45) NC	0/120 (92) 0.6183	1/59 (49) 0.3475	0/60 (51) NC	0/60 (49) NC
	M-Malignant Ganglioneuroma	0/60 (47) NC	0/60 (45) NC	0/120 (92) 0.2033	0/59 (49) NC	0/60 (51) NC	1/60 (49) 0.3475
Body, Whole/Cav	B-Hemangioma	1/60 (47) NC	1/60 (45) NC	2/120 (92) 0.5798	2/60 (49) 0.4329	1/60 (51) 0.7368	1/60 (49) 0.7254
	M-Hemangiosarcoma	0/60 (47) NC	0/60 (45) NC	0/120 (92) 0.0609	1/60 (49) 0.3475	0/60 (51) NC	2/60 (50) 0.1224
	M-Histiocytic Sarcoma	2/60 (47) NC	1/60 (45) NC	3/120 (93) 0.6136	0/60 (49) 1.0000	0/60 (51) 1.0000	1/60 (50) 0.8252
	M-Lymphosarcoma	1/60 (47) NC	1/60 (46) NC	2/120 (92) 0.5180	1/60 (49) 0.7254	1/60 (52) 0.7423	1/60 (49) 0.7254
Brain	B-Granular Cell Tumor	0/60 (47) NC	0/60 (45) NC	0/120 (92) 0.4958	1/60 (50) 0.3521	1/60 (51) 0.3566	0/60 (49) NC
	M-Malignant Astrocytoma	0/60 (47) NC	0/60 (45) NC	0/120 (92) 0.1904	1/60 (49) 0.3475	1/60 (52) 0.3611	1/60 (50) 0.3521
	M-Meningeal Sarcoma	1/60 (48) NC	1/60 (46) NC	2/120 (93) 1.0000	0/60 (49) 1.0000	0/60 (51) 1.0000	0/60 (49) 1.0000
Cervix	B-Polyp, Endometrial Stromal	2/60 (47) NC	0/60 (45) NC	2/120 (92) 0.5022	0/60 (49) 1.0000	0/60 (51) 1.0000	1/60 (50) 0.7312
	M-Leiomyosarcoma	0/60 (47) NC	0/60 (45) NC	0/120 (92) 0.6077	2/60 (50) 0.1224	1/60 (51) 0.3566	0/60 (49) NC
	M-Sarcoma, Endometrial Strom	0/60 (47) NC	1/60 (45) NC	1/120 (92) 1.0000	0/60 (49) 1.0000	0/60 (51) 1.0000	0/60 (49) 1.0000
Colon	M-Leiomyosarcoma	0/59 (47) NC	0/60 (45) NC	0/119 (91) 0.4167	0/60 (49) NC	1/60 (51) 0.3592	0/60 (49) NC
Eye	M-Fibrosarcoma	0/60 (47) NC	0/60 (45) NC	0/120 (92) 0.4174	0/60 (49) NC	1/60 (52) 0.3611	0/60 (49) NC
Gl, Zymbal's	M-Carcinoma	0/60 (47) NC	1/60 (45) NC	1/120 (92) 1.0000	0/60 (49) 1.0000	0/60 (51) 1.0000	0/60 (49) 1.0000
Heart	M-Endocardial Schwannoma	0/60 (47) NC	0/60 (45) NC	0/120 (92) 0.2033	0/60 (49) NC	0/60 (51) NC	1/60 (49) 0.3475

Female Rats Poly-3 Test

Organ Name	Tumor Name	0 mg Control 1 (N=60)	0 mg Control 2 (N=60)	0 mg (N=120) Control 1+2 P - Trend	10 mg Low (N=60) P -CC vs. L	30 mg Med (N=60) P -CC vs. M	100 mg High (N=60) P - CC vs. H
Jejunum	M-Leiomyosarcoma	0/58 (46) NC	1/60 (45) NC	1/118 (91) 1.0000	0/60 (49) 1.0000	0/60 (51) 1.0000	0/59 (49) 1.0000
Liver	B-Adenoma, Hepatocellular	1/60 (47) NC	0/60 (45) NC	1/120 (92) 0.0256	1/60 (49) 0.5759	3/60 (51) 0.1297	4/60 (50) 0.0520
	M-Carcinoma, Hepatocellular	0/60 (47) NC	1/60 (45) NC	1/120 (92) 1.0000	0/60 (49) 1.0000	0/60 (51) 1.0000	0/60 (49) 1.0000
Lung	M-Carcinoma, Bronchiolar-Alv	0/60 (47) NC	0/60 (45) NC	0/120 (92) 0.2033	0/60 (49) NC	0/60 (51) NC	1/60 (49) 0.3475
Mammary, Female	B-Fibroadenoma	3/59 (46) NC	6/59 (46) NC	9/118 (92) 0.7977	10/60 (51) 0.0824	6/59 (52) 0.4727	4/60 (50) 0.7385
	M-Carcinoma	4/59 (46) NC	3/59 (45) NC	7/118 (91) 0.6606	4/60 (49) 0.5797	6/59 (51) 0.3016	3/60 (51) 0.7670
Ovary	B-Granulosa/Theca Cell Tumor	1/60 (47) NC	0/60 (45) NC	1/120 (92) 0.3474	1/60 (49) 0.5759	2/60 (51) 0.2895	1/60 (49) 0.5759
	M-Fibrosarcoma	0/60 (47) NC	1/60 (45) NC	1/120 (92) 1.0000	0/60 (49) 1.0000	0/60 (51) 1.0000	0/60 (49) 1.0000
	M-Yolk Sac Carcinoma	1/60 (47) NC	0/60 (45) NC	1/120 (92) 1.0000	0/60 (49) 1.0000	0/60 (51) 1.0000	0/60 (49) 1.0000
Pancreas	B-Adenoma, Islet Cell	0/60 (47) NC	1/60 (45) NC	1/120 (92) 0.8553	1/60 (49) 0.5759	0/60 (51) 1.0000	0/60 (49) 1.0000
	M-Carcinoma, Islet Cell	0/60 (47) NC	0/60 (45) NC	0/120 (92) 0.8081	3/60 (50) 0.0420*	0/60 (51) NC	0/60 (49) NC
Pituitary	B-Adenoma	38/60 (54) NC	37/60 (50) NC	75/120 (105) 0.9652	41/60 (54) 0.3417	37/60 (55) 0.7672	32/60 (54) 0.9571
	B-Adenoma, Pars Nervosa	0/60 (47) NC	0/60 (45) NC	0/120 (92) 0.2066	0/60 (49) NC	0/60 (51) NC	1/60 (50) 0.3521
	B-Adenoma, Pars Intermedia	0/60 (47) NC	0/60 (45) NC	0/120 (92) 0.2033	0/60 (49) NC	0/60 (51) NC	1/60 (49) 0.3475
	M-Carcinoma	0/60 (47) NC	0/60 (45) NC	0/120 (92) 0.4149	0/60 (49) NC	1/60 (51) 0.3566	0/60 (49) NC
Skin/Subcutis	B-Keratoacanthoma	1/60 (47) NC	0/60 (45) NC	1/120 (92) 1.0000	0/60 (49) 1.0000	0/60 (51) 1.0000	0/60 (49) 1.0000
	M-Fibrosarcoma	0/60 (47) NC	0/60 (45) NC	0/120 (92) 0.1365	0/60 (49) NC	2/60 (52) 0.1288	1/60 (50) 0.3521
	M-Liposarcoma	0/60 (47) NC	1/60 (46) NC	1/120 (92) 1.0000	0/60 (49) 1.0000	0/60 (51) 1.0000	0/60 (49) 1.0000
Spleen	B-Leiomyoma	0/60 (47) NC	0/60 (45) NC	0/120 (92) 0.6183	1/60 (49) 0.3475	0/60 (51) NC	0/60 (49) NC

Female Rats Poly-3 Test

Organ Name	Tumor Name	0 mg Control 1 (N=60)	0 mg Control 2 (N=60)	0 mg (N=120) Control 1+2 P - Trend	10 mg Low (N=60) P -CC vs. L	30 mg Med (N=60) P -CC vs. M	100 mg High (N=60) P - CC vs. H
Stomach, Nonglandular	B-Papilloma, Squamous Cell	0/60 (47) NC	0/60 (45) NC	0/120 (92) 0.2033	0/60 (49) NC	0/60 (51) NC	1/60 (49) 0.3475
	M-Leiomyosarcoma	0/60 (47) NC	0/60 (45) NC	0/120 (92) 0.6183	1/60 (49) 0.3475	0/60 (51) NC	0/60 (49) NC
Thymus	B-Thymoma	1/57 (45) NC	1/59 (44) NC	2/116 (88) 0.8799	3/57 (47) 0.2287	2/60 (51) 0.4676	0/60 (49) 1.0000
	M-Malignant Thymoma	1/57 (44) NC	1/59 (44) NC	2/116 (88) 0.2646	1/57 (48) 0.7324	1/60 (51) 0.7495	2/60 (49) 0.4511
Thyroid	B-Adenoma, C-Cell	6/60 (47) NC	1/60 (45) NC	7/120 (92) 0.2757	3/60 (49) 0.7421	6/60 (52) 0.3073	5/60 (50) 0.4214
	B-Adenoma, Follicular Cell	1/60 (47) NC	1/60 (45) NC	2/120 (92) 0.4233	7/60 (50) 0.0094*	2/60 (52) 0.4572	3/60 (50) 0.2351
	M-Carcinoma, C-Cell	0/60 (47) NC	0/60 (45) NC	0/120 (92) 0.1331	0/60 (49) NC	2/60 (51) 0.1256	1/60 (49) 0.3475
	B-Adenoma/ M-Carcinoma C-Cell	6/60 (47) NC	1/60 (45) NC	7/120 (92) 0.1698	3/60 (49) 0.7421	8/60 (52) 0.1194	6/60 (50) 0.2819
	M-Carcinoma, Follicular Cell	0/60 (47) NC	0/60 (45) NC	0/120 (92) 0.4965	1/60 (49) 0.3475	1/60 (51) 0.3566	0/60 (49) NC
	B-Adenoma/ M-Carcinoma Follicular	1/60 (47) NC	1/60 (45) NC	2/120 (92) 0.4767	8/60 (50) 0.0037*	3/60 (52) 0.2495	3/60 (50) 0.2351
Uterus	B-Adenoma	0/60 (47) NC	0/60 (45) NC	0/120 (92) 0.2033	0/60 (49) NC	0/60 (51) NC	1/60 (49) 0.3475
	B-Leiomyoma	1/60 (47) NC	0/60 (45) NC	1/120 (92) 1.0000	0/60 (49) 1.0000	0/60 (51) 1.0000	0/60 (49) 1.0000
	B-Polyp, Endometrial Stromal	0/60 (47) NC	7/60 (46) NC	7/120 (93) 0.3384	5/60 (49) 0.4001	6/60 (52) 0.3003	5/60 (49) 0.4001
	M-Carcinoma	1/60 (47) NC	5/60 (46) NC	6/120 (93) 0.9745	3/60 (49) 0.6577	3/60 (52) 0.6895	0/60 (49) 1.0000
	M-Carcinoma, Adenosquamous	0/60 (47) NC	0/60 (45) NC	0/120 (92) 0.4149	0/60 (49) NC	1/60 (51) 0.3566	0/60 (49) NC
	M-Leiomyosarcoma	0/60 (47) NC	1/60 (45) NC	1/120 (92) 1.0000	0/60 (49) 1.0000	0/60 (51) 1.0000	0/60 (49) 1.0000
	M-Sarcoma, Endometrial Stromal	2/60 (48) NC	0/60 (45) NC	2/120 (92) 0.5557	1/60 (50) 0.7312	0/60 (51) 1.0000	1/60 (49) 0.7254
	B-Polyp/ M-Sarcoma, Endometrial Stromal	2/60 (48) NC	7/60 (46) NC	9/120 (93) 0.5014	6/60 (50) 0.4332	6/60 (52) 0.4641	5/60 (49) 0.5676

Female Rats Poly-3 Test

Organ Name	Tumor Name	0 mg Control 1 (N=60)	0 mg Control 2 (N=60)	0 mg (N=120) Control 1+2 P - Trend	10 mg Low (N=60) P -CC vs. L	30 mg Med (N=60) P -CC vs. M	100 mg High (N=60) P - CC vs. H
Vagina	B-Leiomyoma	0/60 (47) NC	0/60 (45) NC	0/120 (92) 0.6198	1/60 (50) 0.3521	0/60 (51) NC	0/60 (49) NC
	B-Polyp, Stromal	0/60 (47) NC	0/60 (45) NC	0/120 (92) 0.0420	0/60 (49) NC	0/60 (51) NC	2/60 (50) 0.1224
Whole Body (Multiple Organs)	Leiomyoma / Leiomyosarcoma	1/60 (47) NC	2/60 (45) NC	3/120 (92) 0.9490	5/60 (50) 0.1021	2/60 (51) 0.5872	0/60 (49) 1.0000

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.
*: Statistically significant at 0.005 and 0.025 level for common and rare tumor or 0.01 and 0.05 level for common and rare tumors for tests of dose response relationship and pairwise comparison, respectively

Figure 1A: Kaplan-Meier Survival Curves for
Male Rats

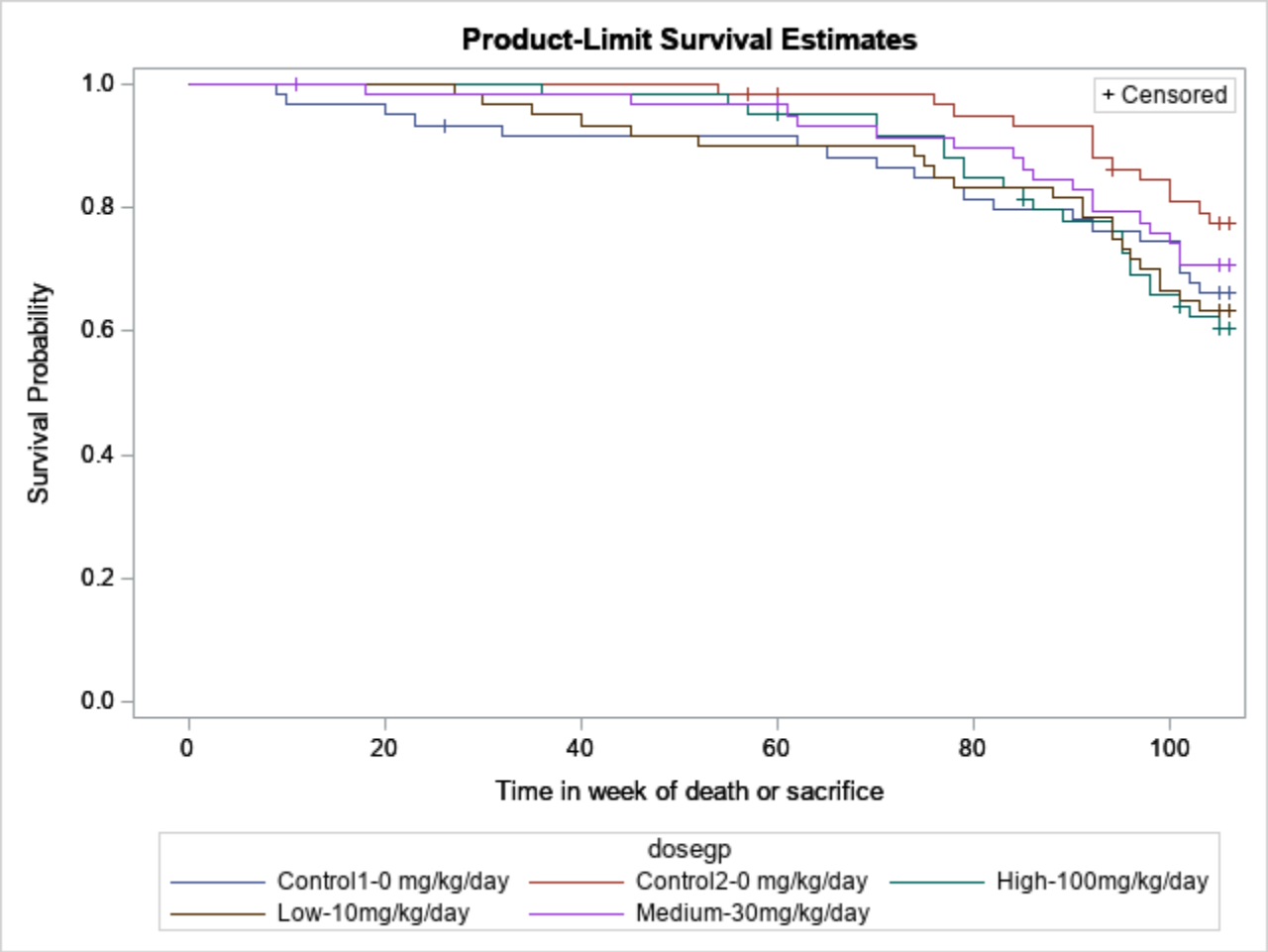


Figure 1B: Kaplan-Meier Survival Curves **for Female Rats**

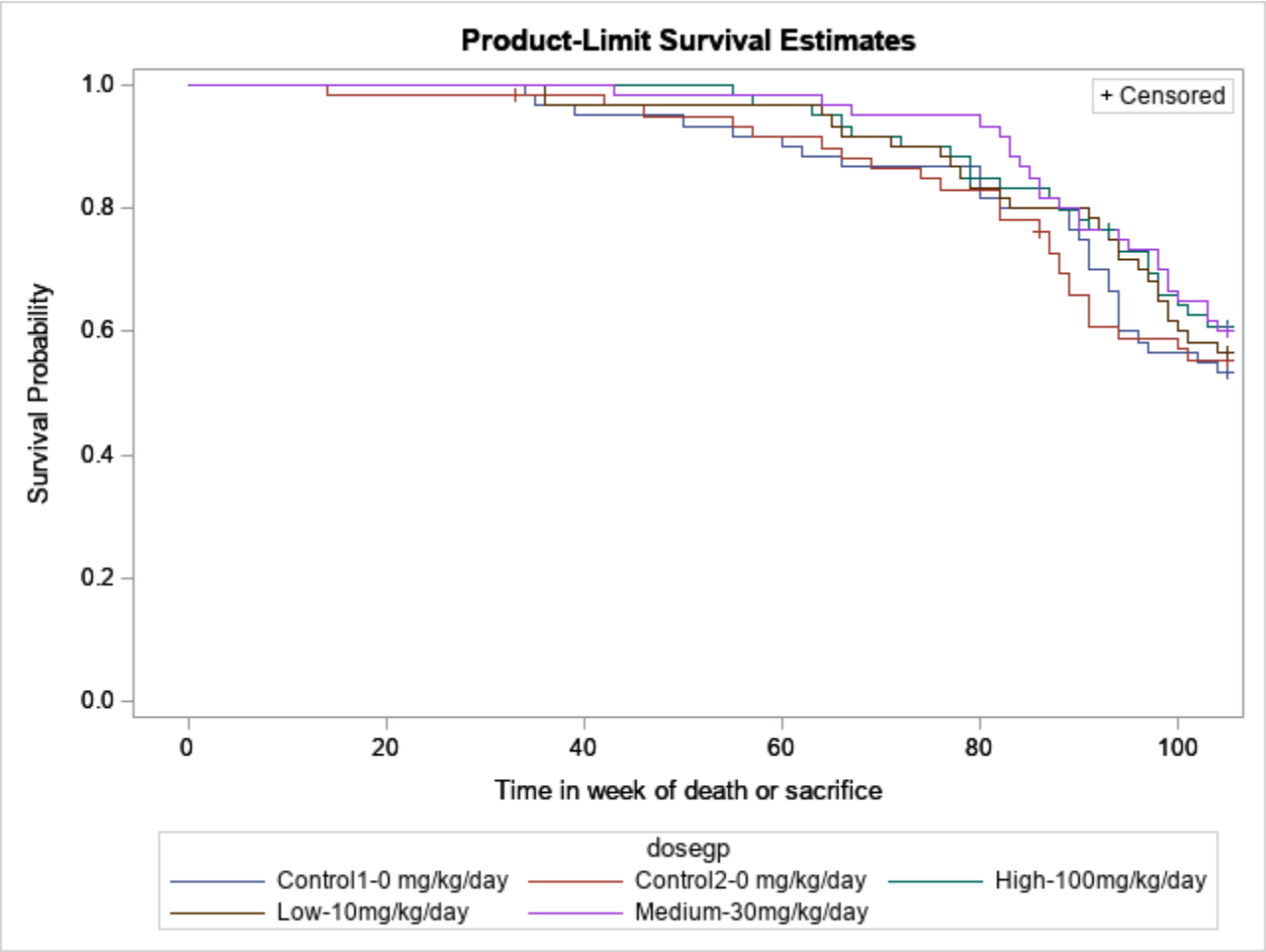


Table4A: Intercurrent Mortality Rate
Male Mice

	0mg|kg|day Veh. Cont		0mg|kg|day Water Cont.		25 mg|kg|day Low		75 mg|kg|day Med		150 mg|kg|day High	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	4	6.67	5	8.33	5	8.33	7	8.97	11	14.29
53 - 78	12	26.67	13	30.00	6	18.33	10	21.79	19	38.96
79 - 92	3	31.67	5	38.33	8	31.67	10	34.62	8	49.35
93 - 105	4	38.33	8	51.67	7	43.33	15	53.85	5	55.84
ADD	.	.	.	.	.	.	1	1.28	.	.
Ter. Sac.	37	61.67	29	48.33	34	56.67	35	44.87	34	44.16
Total	60	100.00	60	100.00	60	100.00	78	100.00	77	100.00

Animals were assigned to the terminal sacrifice strata based on the death or sacrifice status recorded
ADD: accidental death

Table4B: Intercurrent Mortality Rate
Female Mice

	0mg|kg|day Veh. Cont		0mg|kg|day Water Cont.		25 mg|kg|day Low		75 mg|kg|day Med		150 mg|kg|day High	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 52	2	3.33	3	5.00	6	10.00	4	4.94	10	13.51
53 - 78	15	28.33	8	18.33	6	20.00	14	22.22	21	41.89
79 - 92	6	38.33	8	31.67	10	36.67	12	37.04	9	54.05
93 - 105	9	53.33	10	48.33	13	58.33	14	54.32	6	62.16
ADD	.	.	.	.	.	.	.	.	6	8.11
Ter. Sac.	28	46.67	31	51.67	25	41.67	37	45.68	22	29.73
Total	60	100.00	60	100.00	60	100.00	81	100.00	74	100.00

Animals were assigned to the terminal sacrifice strata based on the death or sacrifice status recorded
ADD: accidental death

Table 5A: Intercurrent Mortality Comparison for
Male Mice

Test Statistics	P-value for Combined Cont. Low, Med, high	P-value for Combined Cont. vs Low	P-value for Combined Cont. vs Med	P-value for Combined Cont. vs High
Dose-Response (Likelihood Ratio)	0.0503	0.7131	0.3703	0.0995
Homogeneity (Log-Rank)	0.2170	0.7132	0.3648	0.0933

Table 5B: Intercurrent Mortality Comparison for
Female Mice

Test Statistics	P-value for Combined Cont. Low, Med, high	P-value for Combined Cont. vs Low	P-value for Combined Cont. vs Med	P-value for Combined Cont. vs High
Dose-Response (Likelihood Ratio)	0.0103*	0.3666	0.6940	0.0063*
Homogeneity (Log-Rank)	0.0235*	0.3574	0.6909	0.0046*

* = statistically significant at the 0.05 significance level

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and the pairwise Comparisons

Male Mice Poly-3 Test

Organ Name	Tumor Name	0 mg Control 1 (N=60)	0 mg Control 2 (N=60)	0 mg (N=120) Control 1+2 P - Trend	25 mg Low (N=60) P - CC vs. L	75 mg Med (N=78) P -CC vs. M	150 mg High (N=77) P - CC vs. H
Adrenal Cortex	Adenoma	2/60 (45) NC	3/58 (40) NC	5/118 (85) 0.1191	6/59 (45) 0.1321	5/78 (57) 0.3668	7/77 (50) 0.1006
	Carcinoma	0/60 (45) NC	1/58 (40) NC	1/118 (85) 0.6924	0/59 (45) 1.0000	1/78 (56) 0.6383	0/77 (48) 1.0000
Adrenal Medulla	Pheochromocytoma	1/60 (45) NC	0/58 (40) NC	1/118 (85) 0.6110	0/58 (44) 1.0000	2/78 (57) 0.3530	0/75 (48) 1.0000
Bone, Sternum	Hemangioma	0/60 (45) NC	0/60 (42) NC	0/120 (87) 0.1992	0/60 (46) NC	0/78 (56) NC	1/76 (47) 0.3507
Brain	Meningioma	0/60 (45) NC	1/60 (42) NC	1/120 (87) 1.0000	0/60 (46) 1.0000	0/78 (56) 1.0000	0/77 (48) 1.0000
Epididymis	Interstitial Cell Adenoma	0/60 (45) NC	0/60 (42) NC	0/120 (87) 0.4412	0/60 (46) NC	1/77 (57) 0.3958	0/76 (48) NC
Gall Bladder	Adenoma	2/56 (43) NC	0/53 (37) NC	2/109 (80) 0.9524	1/53 (43) 0.7285	0/69 (50) 1.0000	0/71 (46) 1.0000
Heart	Hibernoma	0/60 (45) NC	0/60 (42) NC	0/120 (87) 0.2025	0/60 (46) NC	0/78 (56) NC	1/77 (48) 0.3556
Hemolymphoreticular	Histiocytic Sarcoma	1/9 (7) NC	0/7 (4) NC	1/16 (11) 1.0000	0/6 (4) 1.0000	0/4 (2) 1.0000	0/4 (2) 1.0000
	Leukemia	1/9 (7) NC	0/7 (4) NC	1/16 (11) 0.2895	0/6 (4) 1.0000	0/4 (2) 1.0000	1/4 (3) 0.3956
	Lymphoma	6/9 (8) NC	5/7 (6) NC	11/16 (14) 0.2130	5/6 (6) 0.6574	4/4 (4) 0.4461	2/4 (2) 0.6500
	Mesothelioma	0/9 (6) NC	1/7 (5) NC	1/16 (11) 1.0000	0/6 (4) 1.0000	0/4 (2) 1.0000	0/4 (2) 1.0000
Jejunum	Carcinoma	0/60 (45) NC	0/58 (40) NC	0/118 (86) 0.4426	0/58 (45) NC	1/77 (56) 0.3944	0/77 (48) NC
Kidney	Carcinoma	0/60 (45) NC	0/60 (42) NC	0/120 (87) 0.2025	0/60 (46) NC	0/78 (56) NC	1/77 (48) 0.3556
Liver	Hemangioma	0/60 (45) NC	0/60 (42) NC	0/120 (87) 0.2025	0/60 (46) NC	0/78 (56) NC	1/77 (48) 0.3556
	Hemangiosarcoma	3/60 (45) NC	1/60 (42) NC	4/120 (87) 0.0303	2/60 (46) 0.6785	1/78 (57) 0.9232	7/77 (51) 0.0587
	Hepatoblastoma	0/60 (45) NC	0/60 (42) NC	0/120 (87) 0.1912	1/60 (47) 0.3507	2/78 (57) 0.1550	1/77 (49) 0.3603
	Hepatocellular Adenoma	12/60 (46) NC	5/60 (42) NC	17/120 (88) 0.9281	7/60 (47) 0.8085	4/78 (57) 0.9917	6/77 (49) 0.9056

Male Mice Poly-3 Test

Organ Name	Tumor Name	0 mg Control 1 (N=60)	0 mg Control 2 (N=60)	0 mg (N=120) Control 1+2 P - Trend	25 mg Low (N=60) P - CC vs. L	75 mg Med (N=78) P -CC vs. M	150 mg High (N=77) P - CC vs. H
	Hepatocellular Carcinoma	4/60 (45) NC	3/60 (42) NC	7/120 (87) 0.2595	5/60 (47) 0.4171	11/78 (58) 0.0461	5/77 (50) 0.4605
	Hepatocellular Adenoma/ Carcinoma	15/60 (46) NC	7/60 (42) NC	22/120 (88) 0.7096	12/60 (48) 0.5781	13/78 (58) 0.7090	11/77 (51) 0.7450
	Histiocytic Sarcoma	0/60 (45) NC	0/60 (42) NC	0/120 (87) 0.1390	0/60 (46) NC	1/78 (56) 0.3916	1/77 (49) 0.3603
Lung with Bronchi	Bronchiolo-Alveolar Adenocarcinoma	2/60 (46) NC	3/60 (42) NC	5/120 (88) 0.0043*	2/60 (46) 0.7617	9/78 (58) 0.0471	9/77 (49) 0.0218
	Bronchiolo-Alveolar Adenoma	12/60 (48) NC	13/60 (42) NC	25/120 (90) 0.5679	11/60 (48) 0.7936	20/78 (58) 0.2467	12/77 (51) 0.7721
	Bronchiolo-Alveolar Adenoma/Adenocarcinoma	13/60 (48) NC	16/60 (42) NC	29/120 (91) 0.1569	13/60 (48) 0.7807	26/78 (60) 0.1041	19/77 (52) 0.3485
	Mesothelioma	1/60 (45) NC	0/60 (42) NC	1/120 (87) 0.6888	0/60 (46) 1.0000	1/78 (57) 0.6367	0/77 (48) 1.0000
Pancreas	Islet Cell Adenoma	1/60 (45) NC	0/60 (42) NC	1/120 (87) 1.0000	0/59 (45) 1.0000	0/78 (56) 1.0000	0/77 (48) 1.0000
Pituitary Gland	Adenoma	1/59 (45) NC	1/59 (41) NC	2/118 (85) 0.1810	0/59 (46) 1.0000	3/77 (57) 0.3174	2/74 (48) 0.4569
Skeletal Muscle	Hemangiosarcoma	0/60 (45) NC	0/60 (42) NC	0/120 (87) 0.1390	0/60 (46) NC	1/77 (56) 0.3916	1/77 (49) 0.3603
Skin	Sarcoma	0/60 (45) NC	0/58 (40) NC	0/118 (86) 0.6356	1/59 (46) 0.3485	0/78 (56) NC	0/77 (48) NC
Skin/Subcutis	Sarcoma	0/7 (2) NC	0/11 (6) NC	0/18 (8) 0.5789	1/9 (5) 0.3846	0/8 (4) NC	0/6 (2) NC
	Schwannoma	1/7 (2) NC	0/11 (6) NC	1/18 (8) 1.0000	0/9 (5) 1.0000	0/8 (4) 1.0000	0/6 (2) 1.0000
Spleen	Hemangiosarcoma	0/60 (45) NC	0/60 (42) NC	0/120 (87) 0.1157	2/60 (46) 0.1179	1/78 (56) 0.3916	2/77 (48) 0.1247
	Lymphoma	1/60 (45) NC	1/60 (42) NC	2/120 (87) 0.9516	1/60 (46) 0.7235	0/78 (56) 1.0000	0/77 (48) 1.0000
Stomach	Adenoma	2/60 (45) NC	0/60 (42) NC	2/120 (87) 1.0000	0/60 (46) 1.0000	0/78 (56) 1.0000	0/77 (48) 1.0000
	Sarcoma	1/60 (46) NC	0/60 (42) NC	1/120 (88) 1.0000	0/60 (46) 1.0000	0/78 (56) 1.0000	0/77 (48) 1.0000
Testis	Carcinoma	1/60 (46) NC	0/60 (42) NC	1/120 (87) 1.0000	0/60 (46) 1.0000	0/77 (56) 1.0000	0/76 (48) 1.0000
	Hemangioma	1/60 (45) NC	0/60 (42) NC	1/120 (87) 0.4198	0/60 (46) 1.0000	0/77 (56) 1.0000	1/76 (48) 0.5864

Male Mice Poly-3 Test

Organ Name	Tumor Name	0 mg Control 1 (N=60)	0 mg Control 2 (N=60)	0 mg (N=120) Control 1+2 P - Trend	25 mg Low (N=60) P - CC vs. L	75 mg Med (N=78) P -CC vs. M	150 mg High (N=77) P - CC vs. H
	Interstitial Cell Adenoma	2/60 (46) NC	4/60 (42) NC	6/120 (88) 0.3790	6/60 (47) 0.1987	4/77 (57) 0.6052	5/76 (49) 0.3475
Thymus	Lymphoma	0/52 (39) NC	1/46 (32) NC	1/98 (72) 1.0000	0/41 (34) 1.0000	0/63 (45) 1.0000	0/65 (39) 1.0000
	Thymoma	1/52 (40) NC	0/46 (31) NC	1/98 (71) 0.8616	1/41 (35) 0.5535	0/63 (45) 1.0000	0/65 (39) 1.0000
Thyroid Gland	Adenoma	0/60 (45) NC	0/59 (41) NC	0/119 (86) 0.5162	1/59 (45) 0.3435	1/78 (57) 0.3986	0/77 (48) NC
Urinary Bladder	Mesenchymal Tumor	1/60 (45) NC	0/60 (42) NC	1/120 (87) 1.0000	0/60 (46) 1.0000	0/78 (56) 1.0000	0/76 (48) 1.0000
Whole Body	Hemangioma/ Hemangiosarcoma	4/60 (45) NC	1/60 (42) NC	5/120 (87) 0.0002*	4/60 (46) 0.3784	5/78 (58) 0.3632	14/77 (52) 0.0006*

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable
*: Statistically significant at 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and The pairwise comparisons

Female Mice **Poly-3 Test**

Organ Name	Tumor Name	0 mg Control 1 (N=60)	0 mg Control 2 (N=60)	0 mg (N=120) Control 1+2 P - Trend	25 mg Low (N=60) P - C vs. L	75 mg Med (N=81) P - C vs. M	150 mg High (N=74) P - C vs. H
Adrenal Cortex	Adenoma	1/59 (43) NC	1/60 (47) NC	2/119 (90) 0.4987	2/60 (44) 0.3985	2/81 (60) 0.5260	1/74 (40) 0.6716
	Carcinoma	0/59 (43) NC	0/60 (47) NC	0/119 (90) 0.4267	0/60 (43) NC	1/81 (60) 0.4000	0/74 (39) NC
Adrenal Medulla	Pheochromocytoma	1/58 (42) NC	2/60 (47) NC	3/118 (89) 0.7838	2/60 (43) 0.5264	0/81 (60) 1.0000	1/74 (40) 0.7782
Bone Marrow, Femur	Hemangioma	0/60 (44) NC	0/60 (47) NC	0/120 (91) 0.4274	0/60 (43) NC	1/81 (61) 0.4013	0/74 (39) NC
	Plasma Cell Tumor	0/60 (44) NC	0/60 (47) NC	0/120 (91) 0.1674	0/60 (43) NC	0/81 (60) NC	1/74 (39) 0.3000
Brain	Astrocytoma	0/60 (44) NC	0/60 (47) NC	0/120 (91) 0.6111	1/60 (44) 0.3259	0/81 (60) NC	0/74 (39) NC
Cervix	Adenocarcinoma	2/60 (44) NC	0/59 (47) NC	2/119 (90) 1.0000	0/60 (43) 1.0000	0/80 (60) 1.0000	0/74 (39) 1.0000
	Carcinoma	1/60 (44) NC	0/59 (47) NC	1/119 (90) 1.0000	0/60 (43) 1.0000	0/80 (60) 1.0000	0/74 (39) 1.0000
	Histiocytic Sarcoma	0/60 (44) NC	0/59 (47) NC	0/119 (90) 0.6121	1/60 (43) 0.3233	0/80 (60) NC	0/74 (39) NC
	Leiomyoma	2/60 (44) NC	1/59 (47) NC	3/119 (90) 1.0000	0/60 (43) 1.0000	0/80 (60) 1.0000	0/74 (39) 1.0000
	Sarcoma	0/60 (44) NC	1/59 (47) NC	1/119 (90) 0.6961	1/60 (44) 0.5506	1/80 (60) 0.6416	0/74 (39) 1.0000
Gall Bladder	Adenoma	0/56 (42) NC	0/53 (42) NC	0/109 (83) 0.4206	0/57 (41) NC	1/71 (54) 0.3942	0/65 (36) NC
Hemolymphoreticular	Histiocytic Sarcoma	3/17 (13) NC	2/14 (11) NC	5/31 (24) 0.2446	2/19 (14) 0.8233	3/15 (12) 0.5449	2/6 (6) 0.4333
	Leukemia	0/17 (12) NC	0/14 (10) NC	0/31 (22) 0.3522	1/19 (13) 0.3714	1/15 (12) 0.3529	0/6 (5) NC
	Lymphoma	13/17 (16) NC	12/14 (13) NC	25/31 (29) 0.8347	16/19 (18) 0.5817	11/15 (15) 0.9255	4/6 (5) 0.8536
	Mesothelioma	1/17 (12) NC	0/14 (10) NC	1/31 (22) 1.0000	0/19 (13) 1.0000	0/15 (12) 1.0000	0/6 (5) 1.0000
Kidney	Lipoma	0/60 (44) NC	1/60 (47) NC	1/120 (91) 1.0000	0/60 (43) 1.0000	0/81 (60) 1.0000	0/74 (39) 1.0000
Liver	Cholangioma	0/60 (44) NC	0/60 (47) NC	0/120 (91) 0.4274	0/60 (43) NC	1/81 (61) 0.4013	0/74 (39) NC

Female Mice Poly-3 Test

Organ Name	Tumor Name	0 mg Control 1 (N=60)	0 mg Control 2 (N=60)	0 mg (N=120) Control 1+2 P - Trend	25 mg Low (N=60) P - C vs. L	75 mg Med (N=81) P - C vs. M	150 mg High (N=74) P - C vs. H
	Hemangioma	0/60 (44) NC	0/60 (47) NC	0/120 (91) 0.4274	0/60 (43) NC	1/81 (61) 0.4013	0/74 (39) NC
	Hemangiosarcoma	0/60 (44) NC	2/60 (47) NC	2/120 (91) 0.5547	0/60 (43) 1.0000	0/81 (60) 1.0000	1/74 (39) 0.6604
	Hepatocellular Adenoma	0/60 (44) NC	3/60 (47) NC	3/120 (91) 0.8141	0/60 (43) 1.0000	2/81 (61) 0.6688	0/74 (39) 1.0000
	Hepatocellular Carcinoma	0/60 (44) NC	1/60 (47) NC	1/120 (91) 0.5562	0/60 (43) 1.0000	2/81 (61) 0.3529	0/74 (39) 1.0000
	Hepatocellular Adenoma/ Carcinoma	0/60 (44) NC	4/60 (47) NC	4/120 (91) 0.7486	0/60 (43) 1.0000	4/81 (62) 0.4168	0/74 (39) 1.0000
Lung with Bronchi	Bronchiolo-Alveolar Adenocarcinoma	4/60 (45) NC	3/60 (47) NC	7/120 (93) 0.6656	3/60 (44) 0.6800	5/81 (62) 0.5657	2/74 (40) 0.8150
	Bronchiolo-Alveolar Adenoma	5/60 (44) NC	8/60 (47) NC	13/120 (91) 0.6881	5/60 (44) 0.7659	13/81 (62) 0.1940	3/74 (40) 0.9221
	Bronchiolo-Alveolar Adenoma/ Adenocarcinoma	9/60 (46) NC	11/60 (47) NC	20/120 (93) 0.7628	8/60 (45) 0.7666	17/81 (63) 0.2738	5/74 (40) 0.9321
	Mesothelioma	0/60 (44) NC	0/60 (47) NC	0/120 (91) 0.1674	0/60 (43) NC	0/81 (60) NC	1/74 (39) 0.3000
Lymph Node, Mesenteric	Hemangioma	0/58 (42) NC	0/59 (46) NC	0/117 (88) 0.4323	0/58 (42) NC	1/79 (60) 0.4054	0/73 (39) NC
Mammary Gland	Carcinoma	0/49 (35) NC	4/46 (38) NC	4/95 (72) 0.8007	1/53 (39) 0.8908	1/72 (56) 0.9471	1/59 (34) 0.8619
Ovary	Adenoma	6/60 (44) NC	0/60 (47) NC	6/120 (91) 0.2042	3/60 (44) 0.6103	2/79 (60) 0.8972	5/74 (40) 0.2135
	Granular Cell Tumor	0/60 (44) NC	0/60 (47) NC	0/120 (91) 0.4224	0/60 (43) NC	1/79 (59) 0.3933	0/74 (39) NC
	Granulosa Cell Tumor	1/60 (44) NC	2/60 (47) NC	3/120 (91) 0.6982	2/60 (44) 0.5267	1/79 (60) 0.8716	1/74 (40) 0.7719
	Hemangioma	1/60 (44) NC	0/60 (47) NC	1/120 (91) 0.6915	1/60 (43) 0.5405	1/79 (59) 0.6336	0/74 (39) 1.0000
	Hemangiosarcoma	0/60 (44) NC	2/60 (48) NC	2/120 (92) 0.4441	0/60 (43) 1.0000	1/79 (60) 0.7811	1/74 (40) 0.6648
	Luteoma	2/60 (44) NC	2/60 (47) NC	4/120 (91) 0.9494	0/60 (43) 1.0000	1/79 (59) 0.9214	0/74 (39) 1.0000
	Teratoma	0/60 (44) NC	1/60 (47) NC	1/120 (91) 1.0000	0/60 (43) 1.0000	0/79 (59) 1.0000	0/74 (39) 1.0000
	Thecoma	1/60 (44) NC	0/60 (47) NC	1/120 (91) 1.0000	0/60 (43) 1.0000	0/79 (59) 1.0000	0/74 (39) 1.0000

Female Mice Poly-3 Test

Organ Name	Tumor Name	0 mg Control 1 (N=60)	0 mg Control 2 (N=60)	0 mg (N=120) Control 1+2 P - Trend	25 mg Low (N=60) P - C vs. L	75 mg Med (N=81) P - C vs. M	150 mg High (N=74) P - C vs. H
Pancreas	Adenoma	2/60 (44) NC	0/60 (47) NC	2/120 (91) 0.7043	0/60 (43) 1.0000	2/81 (61) 0.5282	0/74 (39) 1.0000
	Islet Cell Adenoma	0/60 (44) NC	0/60 (47) NC	0/120 (91) 0.4274	0/60 (43) NC	1/81 (61) 0.4013	0/74 (39) NC
Pituitary Gland	Adenoma	1/59 (43) NC	4/60 (47) NC	5/119 (90) 0.8962	3/59 (43) 0.5095	4/81 (60) 0.5191	0/74 (39) 1.0000
Rectum	Leiomyosarcoma	0/58 (42) NC	0/59 (46) NC	0/117 (89) 0.4310	0/60 (43) NC	1/81 (61) 0.4067	0/74 (39) NC
Skin	Sarcoma	0/60 (44) NC	0/60 (47) NC	0/120 (91) 0.4224	0/60 (43) NC	1/80 (59) 0.3933	0/74 (39) NC
Skin/Subcutis	Hemangioma	0/8 (5) NC	1/10 (7) NC	1/18 (12) 1.0000	0/2 (2) 1.0000	0/6 (3) 1.0000	0/6 (3) 1.0000
	Hemangiosarcoma	1/8 (5) NC	1/10 (7) NC	2/18 (12) 1.0000	0/2 (2) 1.0000	0/6 (3) 1.0000	0/6 (3) 1.0000
	Keratoacanthoma	0/8 (5) NC	1/10 (7) NC	1/18 (12) 1.0000	0/2 (2) 1.0000	0/6 (3) 1.0000	0/6 (3) 1.0000
	Osteosarcoma	0/8 (5) NC	1/10 (7) NC	1/18 (12) 1.0000	0/2 (2) 1.0000	0/6 (3) 1.0000	0/6 (3) 1.0000
	Papilloma	0/8 (5) NC	1/10 (7) NC	1/18 (12) 1.0000	0/2 (2) 1.0000	0/6 (3) 1.0000	0/6 (3) 1.0000
	Sarcoma	0/8 (5) NC	0/10 (7) NC	0/18 (12) 0.1500	0/2 (2) NC	0/6 (3) NC	1/6 (3) 0.2000
Spleen	Hemangiosarcoma	0/60 (44) NC	1/60 (47) NC	1/120 (91) 1.0000	0/60 (43) 1.0000	0/81 (60) 1.0000	0/74 (39) 1.0000
	Lymphoma	0/60 (44) NC	0/60 (47) NC	0/120 (91) 0.6094	1/60 (43) 0.3209	0/81 (60) NC	0/74 (39) NC
Stomach	Papilloma	0/60 (44) NC	0/60 (47) NC	0/120 (91) 0.4249	0/60 (43) NC	1/81 (60) 0.3974	0/74 (39) NC
Thymus	Thymoma	1/51 (37) NC	0/55 (43) NC	1/106 (80) 0.6542	0/55 (39) 1.0000	1/66 (48) 0.6112	0/65 (35) 1.0000
Tongue	Carcinoma	0/60 (44) NC	0/60 (47) NC	0/120 (91) 0.6094	1/60 (44) 0.3259	0/80 (59) NC	0/74 (39) NC
Urinary Bladder	Papilloma	0/60 (44) NC	0/60 (47) NC	0/120 (91) 0.1674	0/60 (43) NC	0/80 (60) NC	1/74 (39) 0.3000
Uterus	Adenocarcinoma	0/60 (44) NC*	0/60 (47) NC	0/120 (91) 0.0109*	1/60 (43) 0.3209	1/81 (61) 0.4013	3/74 (40) 0.0270*
	Adenoma	0/60 (44) NC	0/60 (47) NC	0/120 (91) 0.4274	0/60 (43) NC	1/81 (61) 0.4013	0/74 (39) NC

Female Mice Poly-3 Test

Organ Name	Tumor Name	0 mg Control 1 (N=60)	0 mg Control 2 (N=60)	0 mg (N=120) Control 1+2 P - Trend	25 mg Low (N=60) P - C vs. L	75 mg Med (N=81) P - C vs. M	150 mg High (N=74) P - C vs. H
	Endometrial Stromal Polyp	4/60 (44) NC	3/60 (47) NC	7/120 (92) 0.0814	2/60 (43) 0.8441	6/81 (62) 0.4315	6/74 (41) 0.1716
	Endometrial Stromal Sarcoma	1/60 (44) NC	2/60 (47) NC	3/120 (91) 0.4390	1/60 (43) 0.7919	0/81 (60) 1.0000	2/74 (40) 0.4845
	Endometrial Stromal Sarcoma/ Polyp	5/60 (44) NC	5/60 (48) NC	10/120 (92) 0.0887	3/60 (43) 0.8483	6/81 (62) 0.6895	8/74 (41) 0.1425
	Hemangioma	1/60 (45) NC	0/60 (47) NC	1/120 (91) 1.0000	0/60 (43) 1.0000	0/81 (60) 1.0000	0/74 (39) 1.0000
	Hemangiosarcoma	0/60 (44) NC	1/60 (48) NC	1/120 (91) 0.0782	2/60 (44) 0.2477	0/81 (60) 1.0000	3/74 (41) 0.0887
	Histiocytic Sarcoma	0/60 (44) NC	1/60 (48) NC	1/120 (91) 0.0776	0/60 (43) 1.0000	2/81 (60) 0.3472	2/74 (40) 0.2208
	Leiomyoma	1/60 (44) NC	0/60 (47) NC	1/120 (91) 0.2104	2/60 (43) 0.2411	0/81 (60) 1.0000	2/74 (40) 0.2208
	Leiomyosarcoma	0/60 (44) NC	0/60 (47) NC	0/120 (91) 0.6111	1/60 (44) 0.3259	0/81 (60) NC	0/74 (39) NC
Vagina	Fibroma	1/59 (43) NC	0/60 (47) NC	1/119 (90) 1.0000	0/59 (43) 1.0000	0/80 (60) 1.0000	0/74 (39) 1.0000
Whole Body	Hemangioma/ Hemangiosarcoma	3/60 (45) NC	8/60 (50) NC	11/120 (95) 0.5351	3/60 (44) 0.8820	4/81 (62) 0.9139	5/74 (42) 0.5810

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ= total number of animals observed;
NC = Not calculable;
*: Statistically significant at 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

Figure 2A: Kaplan-Meier Survival Curves for

Male Mice

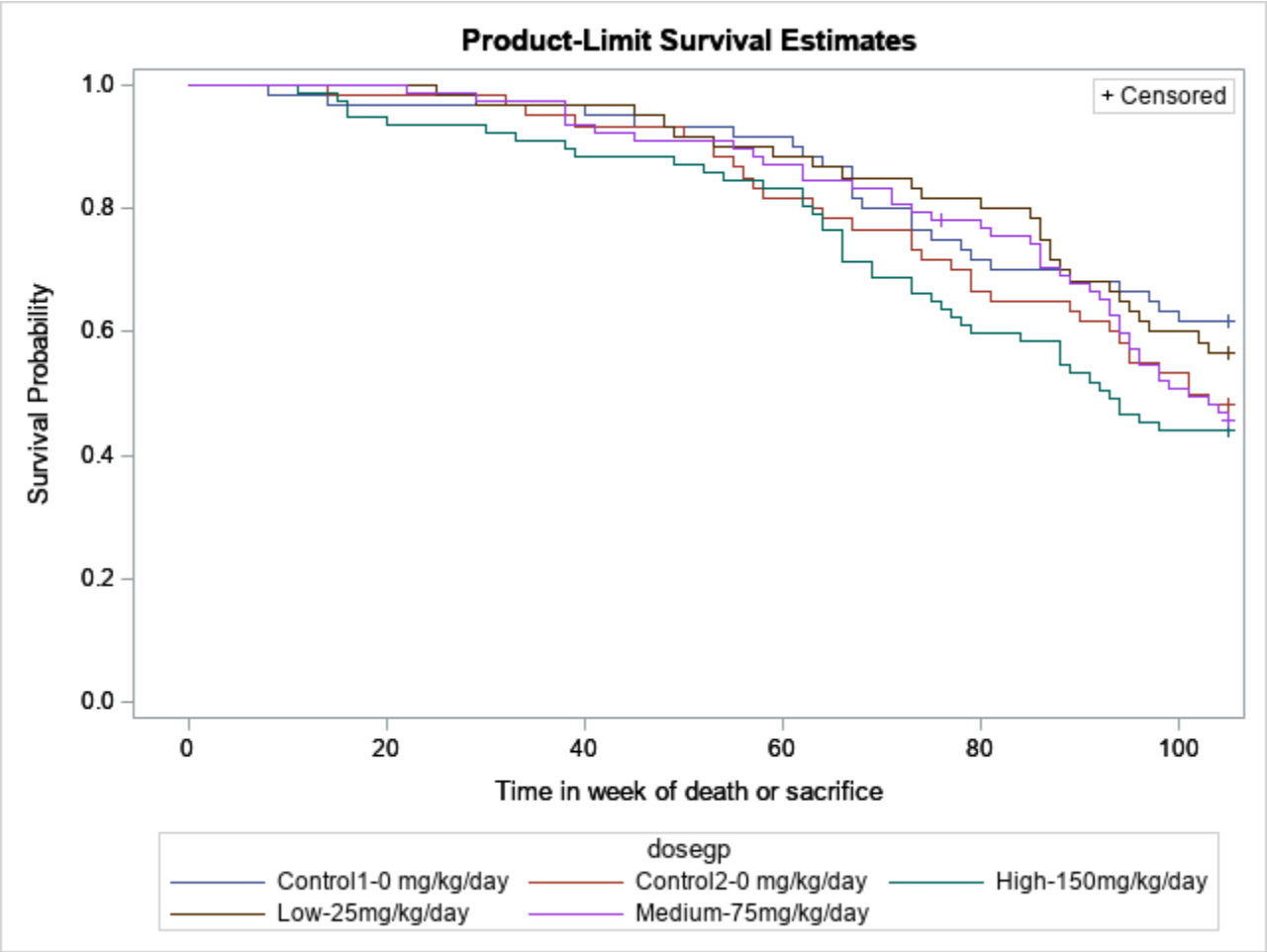
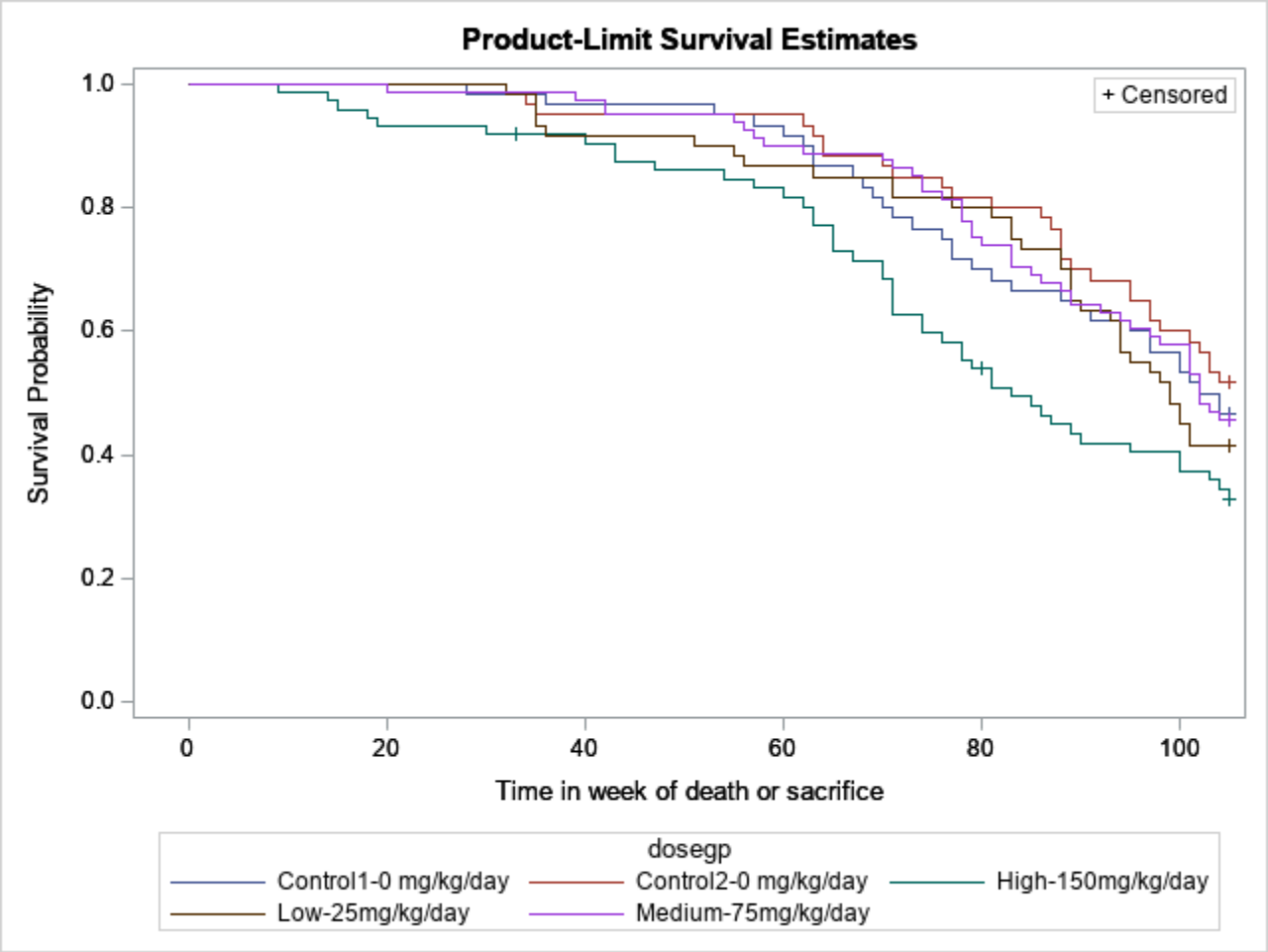


Figure 2B: Kaplan-Meier Survival Curves for
Female Mice



6. References:

1. Bailer AJ, Portier CJ (1988). "Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples." *Biometrics*, 44, 417-431.

2. Bieler, G. S. and Williams, R. L. (1993). "Ratio estimates, the delta method, and quantal response tests for increased carcinogenicity". *Biometrics* 49, 793-801.

3. Gebregziabher M, Hoel D (2009) Applications of the poly-k statistical test to life-time cancer bioassay studies. Hum Ecol Risk Assess 15(5):858{875.

4. Guidance for Industry. Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Statues of Pharmaceuticals (Draft Guidance). U.S. Department of Health and Human Services, Food and Drug Administation, Center for Drug Evaluation and Research (CDER), May 2001.

5. Moon H, Ahn H, Kodell RL, Lee JJ (2003) Estimation of k for the poly-k test with application to animal carcinogenicity studies. Statistics in Medicine 22(16):2619{2636

6. Peto, R., M.C. Pike, N.E. Day, R.G. Gray, P.N. Lee, S. Parish, J. Peto, Richards, and Wahrendorf, "Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments", Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, Annex to supplement, World Health Organization, Geneva, 311-426, 1980.

7. Portier C, Hedges J, Hoel D (1986) Age-speci_c models of mortality and tumor onset for historical control animals in the national toxicology programs carcinogenicity experiments. Cancer Research 46:4372{4378

8. Rahman M.A. and Lin K.K, "A comparison of False Positive Rates of Peto and Poly-3 Method For Long Term Carcinogenicity Data Analysis Using Multiple Comparison Adjustment Method Suggested by Lin and Rahman" Journal of Biopharmaceutical Statistics, 18: 949-958, 2008.

9. Tarone RE, "Test for trend in life table analysis", Biometrika 1975, 62: 679-82

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MALICK MBODJ
09/07/2021 08:13:54 AM

KARL K LIN
09/07/2021 09:46:42 AM
Concur with review.